Literature Review

Pneumococcal Vaccine in Lung Cancer: A Literature Review

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Abstract

Streptococcus pneumoniae (*S. pneumoniae*) is one of the organisms that cause various diseases with a high burden, and pneumonia is one of the major clinical manifestations. The pneumococcal vaccine, as known, provides immunity against *S. pneumoniae* and consists of two types available in Indonesia: polysaccharide and conjugate vaccines. The polysaccharide vaccine is the 23-valent pneumococcal polysaccharide vaccine (PPSV23), and the conjugate vaccines are the 13-, 15-, and 20-valent pneumococcal conjugate vaccines (PCV13, PCV15, and PCV20). The conjugate vaccine can provide more effective immunity, involving the activation of T cells and memory B cells. By providing effective protection against *S. pneumoniae*, the pneumococcal vaccine reduces community-acquired pneumonia (CAP) hospitalization and improves overall survival, especially in lung cancer patients who have a higher risk of infection with pneumonia. Aside from the pathological condition, cancer treatment, such as chemotherapy, can alter the immune system, thereby increasing the risk of infection. Therefore, the pneumococcal vaccine is recommended for lung cancer patients. Besides that, knowledge of the pneumococcal vaccine is also essential to optimize lung cancer treatment.

Keywords: conjugate vaccine, pneumococcal vaccine, polysaccharide vaccine

INTRODUCTION

Lung cancer is one of the leading causes of cancer death worldwide. Lung cancer was the most common type of cancer among men in Indonesia in 2020, with 34,783 new cases, or 14.1% of all cancer cases. As a cause of death, lung cancer is predicted to be the leading cause of cancer death, contributing to 13.2% of cancer deaths.[1]

Lung cancer patients generally experience a pro-inflammatory condition causing immune dysregulation, making them susceptible to infection; one of these is *Streptococcus pneumoniae* (*S. pneumoniae*). It is a Gram-positive bacterium that can cause various diseases such as pneumonia, bacteremia, and meningitis.[2] he increased susceptibility contributes to a 13.4 times higher incidence of pneumococcal infection in lung cancer patients compared with the healthy population.[3,4]

Therefore, the pneumococcal vaccine is a vaccine designed to develop immunity

against *S. pneumoniae* and is available in two forms: the polysaccharide vaccine (PPSV) and the conjugate vaccine (PCV). Currently, available pneumococcal vaccines include PCV13, PCV15, PPSV23, and PCV20. Vaccination with PCV15 or PCV20 has been recommended to reduce mortality and morbidity from *S. pneumoniae*.[5]

This review article explains information on the mechanism, use, and recommendations for pneumococcal vaccines in lung cancer, based on a literature search conducted in PubMed and Google Scholar using the main keywords 'pneumococcal vaccine' and 'lung cancer'.

PNEUMONIA IN LUNG CANCER

Lower respiratory tract infections are a leading cause of mortality and morbidity worldwide, with 2.38 million deaths in 2016; one type is pneumonia. It is known that fatal cases are increasing in groups with low sociodemographic status, limited access to health facilities, and poor nutritional status.[6]

In addition, the risk of pneumonia also increases in immunocompromised groups, including cancer. This is because lung cancer patients have an increased incidence of pneumococcal infection, thus affecting survival rates.[7] The risk of infection is also known to increase, especially in advanced stages, due to changes in the immune system and lung structure; it is reported to occur in 50–70% of patients. One form is post-obstructive pneumonia, which occurs when airway clearance is reduced due to tumor obstruction, with >50% of advanced-stage patients having endobronchial abnormalities.[8]

Besides that, cancer therapies, such as chemotherapy and radiotherapy, can also affect the immune system, increasing the risk of infection.[9] A study at Persahabatan Hospital in lung cancer patients visiting the emergency department (ED) reported pneumonia in 81% of patients, with a mortality rate of 30.2% in lung cancer patients with pneumonia.[10]

Therefore, a pneumococcal vaccine has been developed. It is derived from *S. pneumoniae*, a spherical Gram-positive bacterium that survives in both aerobic and anaerobic conditions. The bacterium causes pneumonia and has a cell wall composed of a thick peptidoglycan layer and a double phospholipid layer. It possesses a polysaccharide capsule, which is a key factor in pneumococcal virulence, interferes with the immune system's clearance and opsonophagocytic function, and also plays a crucial role in bacterial adhesion. This is the basis for the development of the pneumococcal vaccine.[5,11]

Pneumococci have various serotypes based on the polysaccharides in the outer capsule, and each serotype has distinct characteristics. Currently, there are over ninety pneumococcal serotypes identified, with 62% of invasive pneumococcal infections caused by 10 serotypes.[12,13] Generally, serotypes 1, 4, 5, 7F, 8, 12F, 14, 18C, and 19A are reported to be the

serotypes most frequently causing invasive pneumococcal disease (IPD).[13]

As is known, variations in serotype distribution are also influenced by geographic differences and population characteristics. Common serotypes found in Indonesia include 19F (11%), 23F (10%), 15B/C (8%), and 19A and 14A (each at 4%).[14,15] The large number of serotypes necessitates serotyping.

Serotyping is also very important to assess vaccine efficacy before and after implementation. The two serotyping techniques are serological and molecular. The serological method, or Quellung technique, uses antiserum to determine the serotype of pneumococcal cultures. This method is considered the gold standard. Meanwhile, molecular testing typically uses a polymerase chain reaction (PCR) assay to amplify specific capsular deoxyribonucleic acid (DNA) elements.[12]

Results from serotyping are used for vaccination programs, such as PCV13, which covers 56% of these serotypes, or PCV7, which was originally developed to prevent pneumococcal disease with an estimated coverage of 80% in children.[14–16]

Unfortunately, pneumococcal serotype data in Indonesia are still limited. An epidemiological study in hospitals in 2008–2009 with a population of children aged 28 days to 60 months in Surabaya and Bandung reported an IPD case rate of 0.4–0.5%. The serotypes reported were only 14 and 23F found in Bandung, and 5 found in Surabaya.[15]

In addition, a study conducted in two referral hospitals in Jakarta involving 205 patients with pneumonia, meningitis, and sepsis reported only one patient with serotype 7F in blood culture.[14] A recent study from New York, including 912 patients with community-acquired pneumonia (CAP), also reported that the most common serotype was 7F, with multiple serotypes in a single patient observed in 35% of patients, and a 30-day mortality rate of 31.7% for pneumococcal pneumonia in cancer patients was reported.[17]

PNEUMOCOCCAL VACCINE

Vaccination is a method to induce artificial immunity against a specific disease. Specificity means that the immunity only works against an organism that matches the antigen contained in the vaccine. The specific immune response to vaccines involves the interaction between the humoral immune response involving B lymphocytes and the cellular immune response mediated by T lymphocytes.[5]

Immunity begins when antigens interact with dendritic cells, activating danger receptors, namely pattern recognition receptors (PRRs). Dendritic cells carry antigens to the lymph nodes to present them to T cells. Presentation of antigens by the major histocompatibility complex (MHC) activates T cells through the T-cell receptor (TCR). T cells then stimulate the development of B cells to produce antibodies with high affinity and various antibody isotypes.[18]

Antibody levels increase two weeks after initial exposure due to the activity of

short-lived plasma cells. T cell activation also influences the production of longer-lived memory B cells, which play a role in antibody production upon subsequent exposure to specific antigens and are located in the bone marrow. In addition to antibody production, immunization also activates CD8+ T cells, resulting in the formation of effector CD8+ T cells and memory CD8+ T cells. Effector T cells play a role in eliminating infected cells.[18]

A crucial characteristic of vaccination is the formation of memory cells. Individuals who have been exposed to a specific pathogen will mount a faster and stronger adaptive immune response upon re-exposure to that antigen. This memory capacity increases with the incubation period of a pathogen. Conversely, a short incubation period for a pathogen will not generate adequate immune memory. Therefore, immune memory capacity is a key consideration in vaccination strategies, such as scheduling and administering booster doses.[5,18]

Based on antigen work, conjugate vaccines differ from polysaccharide vaccines because they contain a carrier protein, such as diphtheria toxoid. Conjugate vaccines are immunogenic because they contain polysaccharide and conjugate components that activate T cells and B cells to form high-affinity, long-acting antibodies. T cells recognize the carrier protein, while B cells recognize the polysaccharide. T cells then provide help to B cells, resulting in affinity maturation and the production of plasma cells and memory B cells. This conjugation process aims to increase immunogenicity, thereby stimulating cellular and humoral immunity.[18,19]

On the other hand, polysaccharide vaccines induce plasma cells to produce antibodies through cross-linking with B cell receptors. However, antibody affinity maturation and memory B cell induction do not occur. The difference in immune responses based on T cell involvement underlies the distinction between T-dependent and T-independent immune responses.[18,19] Figure 1 shows the differences in the immune responses of polysaccharides and conjugates.

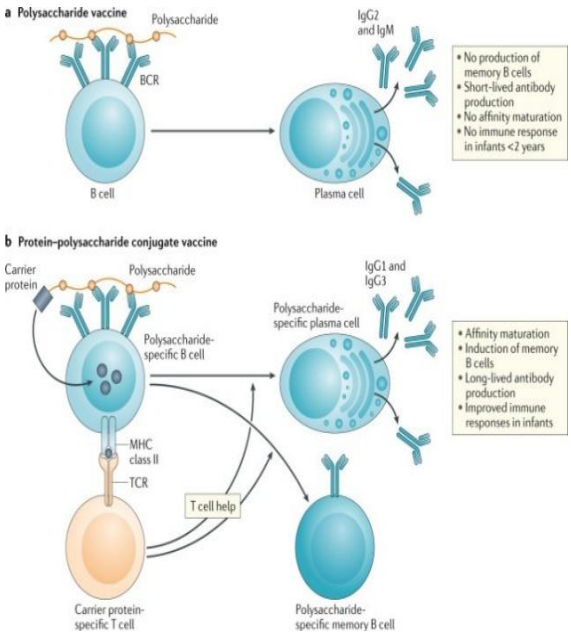


Figure 1. Differences in the immune responses of polysaccharides and conjugates.[18]

The pneumococcal vaccines available in Indonesia are PCV13, PCV15, and PCV20, which are administered intramuscularly at 0.5 mL, and PPSV23, which is administered intramuscularly or subcutaneously. Pneumococcal vaccination recommendations in Indonesia are issued by the Adult Immunization Task Force of

the Indonesian Internal Medicine Specialists Association (*SATGAS Immunisasi Dewasa PAPDI*). The PPSV23 vaccine can be administered to anyone over 50 years of age.[20]

Specifically, the PPSV23 vaccine can be administered to anyone over 50 years of age and is recommended for immunocompromised individuals because these individuals are at risk of infection by a wider variety of serotypes. This is because the PPSV23 vaccine has a broader serotype coverage than PCV, although the immunity it provides is not as strong as that provided by PCV. Therefore, PPSV23 vaccination is intended to build immunity against serotype variations not found in PCV.[20] The serotype composition of each vaccine is shown in Figure 2.

Meanwhile, conjugate vaccines such as PCV13, PCV15, and PCV20 may be used in adults starting at age 18. This vaccine is highly recommended for vulnerable individuals such as those with compromised immune systems or those traveling to areas with a risk of pneumococcal transmission, such as during the Hajj and Umrah pilgrimages. Pneumococcal vaccine administration should consider vaccination history.[5,20]

Individuals who have previously received PPSV23 should still be given the conjugate vaccine with a 1-year interval, while PCV20 does not need to be followed by PPSV23. Individuals who have previously received PCV13 or PCV15 vaccines should be given PCV20 with a 1-year interval. The interval between PPSV and PCV is crucial to prevent a reduced immune response due to immune hyporesponsiveness.[5,20]

If an individual has previously received PCV13/PCV15 and PPSV23, PCV20 can be given with a 5-year interval in individuals aged <65 years with comorbidities such as immunocompromised status, cerebrospinal fluid leaks, or cochlear implants.[5,20] Figure 3 shows recommendations for pneumococcal vaccination in Indonesia.

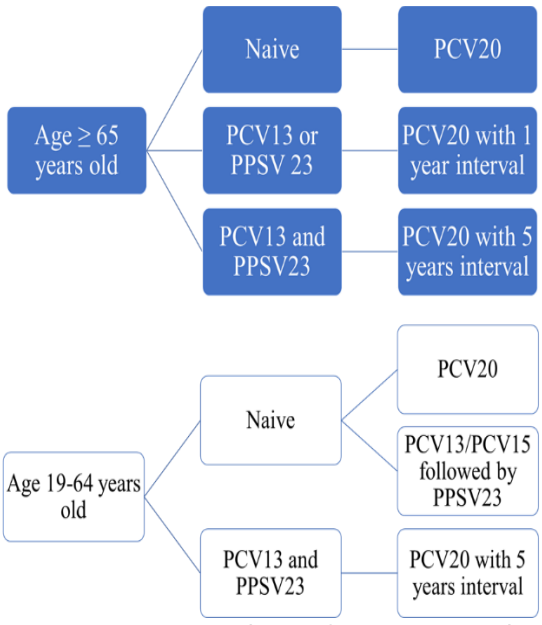


Figure 3. Recommendations for pneumococcal vaccination[5,20]

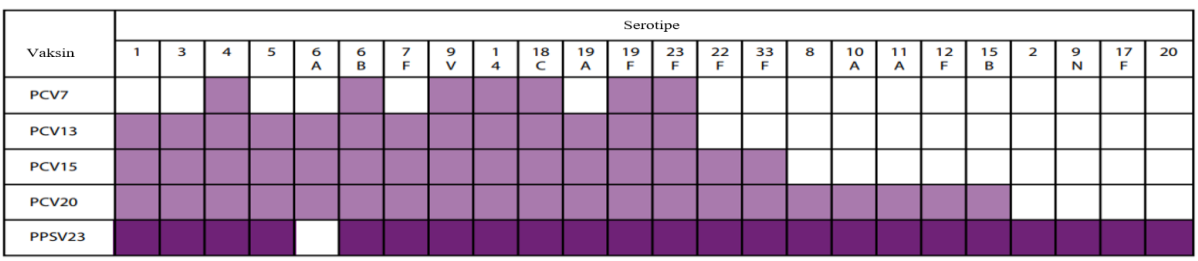


Figure 2. Serotype composition of pneumococcal vaccine[21]

PNEUMOCOCCAL VACCINE EFFICACY IN LUNG CANCER

The increased risk of infection is a significant survival issue for lung cancer patients. Cancer treatments such as chemotherapy or radiation therapy, which affect the immune system, can also contribute to an increased risk of infection in cancer patients. Therefore, vaccination is a crucial preventive measure to prevent infections, including pneumonia. A study of lung cancer patients aged 75 years and older in Taiwan reported a 0.74-fold lower incidence of CAP in the PPSV23 group compared with controls. The PPSV23 group had better 2-year hospitalization rates for CAP and overall survival than controls: 37.1% vs. 55.4% and 46.6% vs. 26.2%, respectively.[9]

Smok-Kalwat et al also evaluated the immunological response to PCV13 in patients with non-small cell lung cancer (NSCLC). The results showed increased plasmablast and antibody levels following vaccination. Thirty days after vaccination, anti-pneumococcal antibody levels in vaccinated NSCLC patients were 4.92-fold higher than before vaccination. Additional analysis revealed that advanced-stage cancer correlated with a worse immunological response than early-stage disease.[22]

Besides that, lung cancer patients had lower anti-pneumococcal antibodies compared with healthy subjects. The healthy group had eightfold higher anti-pneumococcal antibody levels at 30 days after vaccination. These data indicate that vaccination increases antibody levels, although the response in NSCLC patients was lower than in the healthy group.[22]

Clinically, the vaccinated group had no more than two respiratory tract infections per year during the study period. In contrast, the incidence of respiratory tract infections in the unvaccinated group was three to six events per year. However, this study did not show an increase in overall survival at 5-year follow-up. Advanced-stage cancer at the time of initial recruitment may have contributed to this result.[22]

PNEUMOCOCCAL VACCINE RECOMMENDATION IN LUNG CANCER

The increased morbidity and mortality rates associated with CAP in lung cancer highlight the potential of pneumococcal vaccines for lung cancer patients. However, implementation of these vaccines remains limited. In addition, few controlled trials have examined the efficacy of pneumococcal vaccines in lung cancer patients.

Meanwhile, the pneumococcal vaccine is currently not recommended in some European countries, whereas the Infectious Diseases Society of America (IDSA) and the Centers for Disease Control and Prevention (CDC) recommend the pneumococcal vaccine for all cancer patients.[23,24] Even though the IDSA and CDC do not specify cancer types, data suggest that lung and pancreatic cancer are the priorities for pneumococcal vaccination.[25]

A study at a German healthcare facility reported that only 9.4% of lung cancer patients received the complete pneumococcal vaccination. This figure is lower than the 29.5% pneumococcal vaccination coverage in the chronic lung disease population, where a large proportion of patients, 62.2%, did not receive the pneumococcal vaccine.[26]

Optimal timing of vaccination is crucial because of the possibility of immune dysregulation following cancer therapy. Preventive vaccination in adults with malignancies is recommended to be administered 2–4 weeks before cancer treatment.[27] Data from solid organ malignancies suggest that the effectiveness of the pneumococcal vaccine is not affected when it is given before the initiation of cancer treatment. A study in a gastric and colorectal cancer population reported comparable serological responses to PCV13 between the group vaccinated on the first day of chemotherapy and the group vaccinated two weeks before chemotherapy.[28]

Serotype coverage is an important consideration when choosing between PCV and PPSV. Previous studies reported that PCV13 serotypes caused 30% of IPD cases, whereas PPSV23 covered 74% of IPD serotypes. The American Society of Clinical Oncology (ASCO) has provided vaccine-related recommendations for adults with malignancies. Pneumococcal vaccines may be given to individuals aged 19 years and older, either as a single dose of PCV20 or as one dose of PCV15 followed by PPSV23 at an interval of eight weeks.

However, improved serotype coverage and higher immunogenicity have led to a preference for PCV20. It is important to check the patient's vaccination history before PCV20 administration; patients who have received PCV13 need only a one-year interval before receiving PCV20.[27] In addition, the current CDC recommendation is that a single dose of PCV20 is adequate, so an additional dose of PPSV23 is not needed.[29]

INTEGRATING PNEUMOCOCCAL VACCINATION INTO CANCER THERAPY

The potential of vaccination in lung cancer requires further investigation, considering vaccine interaction with cancer therapy such as chemotherapy or immunotherapy. Initially, vaccination had to be given at least two weeks before chemotherapy. For example, a study by Nordoy et al evaluated the response to pneumococcal vaccination given between two courses of chemotherapy in 35 patients with various cancer types. The study reported a satisfactory serological response following PPSV23 vaccination, as measured by the increase in antibody levels.[30]

In addition, a study by Choi et al. also assessed the optimal interval between vaccination and chemotherapy initiation in patients with solid malignancies. This study compared serological responses between the group vaccinated on the first day of chemotherapy and the group vaccinated two weeks before chemotherapy. The results showed no significant difference in serological responses between the two

groups, where immunogenicity was assessed by the geometric mean and fold increase of post-vaccination titers.[28] These studies, which used PCV13 or PPSV23, showed that vaccination still elicits an adequate serological response in patients receiving chemotherapy, and that timing should not be a barrier to vaccination.

Huang et al explain in a case report that an increased immune response follows PCV administration in ALK+ NSCLC. The case was a 60-year-old man with stage IVB NSCLC, who had received 11 months of crizotinib, 24 months of alectinib, and radiotherapy for lumbar metastasis. Vaccination was given three months following radiotherapy. Due to lesion enlargement, the patient underwent lung resection. The results showed a robust immune response in the primary lesion, characterized by a central area of necrosis surrounded by infiltrating immune cells.[31]

That case illustrated that a combination of radiotherapy and PCV may activate host immunity and improve treatment outcome. It was hypothesized that the polysaccharide component of the vaccine triggers an immune response contributing to this effect. However, further research is needed to evaluate whether combination therapy involving vaccination enhances the overall immune response and results in improved clinical outcomes.[31]

Immune-related adverse events (irAEs) should be monitored in patients receiving immune checkpoint inhibitors (ICIs). Theoretically, vaccination is a risk factor for immune-related adverse events. A cohort study including 71 vaccinated patients receiving ICIs showed no significant difference in irAE incidence. Differences in treatment delay and discontinuation were also not significant, with the pneumococcal vaccine being the second most commonly administered vaccine; 8 patients received PCV13 and 19 received PPSV23. The study demonstrated that the use of inactivated vaccines during ICI therapy is safe and well tolerated.[32]

CONCLUSION

Lung cancer patients are among the immunocompromised populations, making them susceptible to pneumonia. One of the most common causes of pneumonia is *S. pneumoniae*. The pneumococcal vaccine is given to build immunity against *S. Pneumoniae*, with two types of pneumococcal vaccines: the polysaccharide vaccine (PPSV23) and the conjugate vaccine (PCV13, PCV15, and PCV20). The polysaccharide vaccine offers broad coverage, although the conjugate vaccine provides stronger immunity. Available evidence suggests pneumococcal vaccination is immunogenic and safe in lung cancer patients, although further prospective studies are needed.

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