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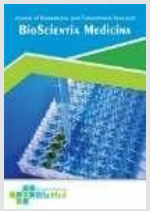

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Aspergillosis in Lung Cancer: A Narrative Literature Review

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A B S T R A C T

Aspergillosis is one of the complications of lung cancer and lung cancer treatment. Diagnosis of Aspergillosis in lung cancer, in general, is still a challenge because clinical symptoms and examination results are not typical, and risk factors often go unnoticed. To simplify the diagnosis of Aspergillosis, several criteria have been created based on the patient's condition, clinical and radiological features, and mycological laboratory examination. Doctors' vigilance still needs to be increased, examination facilities are still limited in certain cities, and diagnostic services have not been integrated, so management is not optimal. This literature review aims to increase doctors' knowledge and awareness regarding aspergillosis in lung cancer, which is an important step to improve the appropriate management of this disease.

1. Introduction

Diseases caused by fungal infections pose a major threat to public health. Opportunistic fungi such as Aspergillus, *Cryptococcus*, *Pneumocystis*, and endemic fungi are the main source of fungal infections in the lungs. Fungal infections are rare in healthy people and can cause life-threatening invasive disease in patients with compromised immune systems.[1] Under certain conditions, this disease causes a high mortality rate, reaching 50-100%.[2] Patient immunocompromised increases from year to year so that the incidence of fungal infections in the lungs also increases.[1] Patients suffering from immunodeficiency disorders such as HIV/AIDS, cancer patients undergoing cytotoxic chemotherapy, patients receiving immunosuppressive therapy such as in bone marrow/solid organ transplantation including patients with long-term neutropenia, high-dose and long-term corticosteroids, acquired immunodeficiency levels advanced and chronic granulomatous disease are patients at risk for developing fungal infections.[1] The most important risk factor is neutropenia, especially when the absolute neutrophil count is less than 500 cells/mm^3, with a mortality rate exceeding 50%.[3]

Malignant disease/cancer is a health problem in Indonesia that has the potential to be the basis for pulmonary aspergillosis. Patients with lung malignancies can experience recurrent fevers due to post-obstruction pneumonia or other lung abnormalities in the form of cavities or lung nodules. Administration of chemotherapy and high doses of corticosteroids is associated with increased pulmonary aspergillosis in malignant patients.[2] Data on pulmonary mycosis in Indonesia is still limited due to various obstacles. Research conducted by Almaududi on non-small cell lung carcinoma (NSCLC) patients

who had not received chemotherapy who were being treated at Persahabatan General Hospital showed that the fungal isolates that grew the most were *Candida albicans* (72.3%) and *Aspergillus niger* (33.8%).[2] Aspergillosis is a complication of lung cancer and lung cancer treatment. A retrospective study conducted by Park S et al. stated that 2.6% of patients with lung cancer had invasive pulmonary aspergillosis (IPA).[3] Jiang et al. reported 8 cases of aspergilloma in lung cancer patients.[4] Guziejko also reported a case of chronic pulmonary aspergillosis (CPA) in lung cancer patients who have received chemoradiotherapy.[5] A case report regarding subacute invasive pulmonary aspergillosis (SIPA*)* in lung cancer patients who had received chemoradiotherapy treatment has also been reported by Wanatabe et al.[6]

Gupta et al. also reported a case of invasive pulmonary aspergillosis in patients with non-small cell lung cancer (NSCLC) who have received durvalumab chemotherapy.[7] Research conducted by Hye Sin et al. described 3430 patients with non-small cell lung cancer. Seven patients who underwent tumor resection surgery were NSCLC and CPA patients, and 56 patients developed CPA after undergoing lung tumor resection.[8] Research conducted by Isra Thristy and Yahwardiah Siregar in 2016 reported the percentage of fungi *Aspergillus sp* as the cause of lung infections is 90%.[9] Aspergillosis is usually diagnosed in patients immunocompromised with other chronic respiratory disorders.[5,10] Diagnosis aspergillosis is difficult to establish because symptoms are nonspecific and are based on clinical, radiological, and microbiological criteria and exclude other, more frequent causes of reported symptoms. An accurate diagnosis is essential to be able to initiate appropriate treatment.[5,11-13] Follow-up after lung cancer treatment is not only monitoring the possibility of tumor recurrence but also identifying possible complications of late infection in patients who have the potential to experience immunosuppression.[5,11] This study aims to increase knowledge and awareness regarding aspergillosis in lung cancer, which is an important step to ensure the governance of the disease properly.

Pathogenesis

Aspergillus sp can survive a wide range of pH and temperature, and its hydrophobic cell walls allow this species to be dispersed efficiently even by small air currents. The characteristics of Aspergillus fumigatus allow this species to be the predominant mold species, causing infections in humans.[14] The small size of the conidia allows penetration into the lower respiratory system and escape mucociliary clearance. Melanin in the cell walls allows *A. fumigatus* to defend against reactive oxygen species (ROS) and phagocytosis. The negatively charged sialic acid on the cell surface allows *A. fumigatus* to effectively bind to basal lamina proteins of lung cells.[14] Aspergillus fumigatus can cause various infections in both immunocompromised and immunocompetent individuals, although conidia can be easily cleared by the host's natural defense mechanisms in the lungs.[13,16] It is estimated that there are 16 million lung infections caused by *A. fumigatus* with outcome which is fatal in hundreds of thousands of patients each year.[17,18] Biosynthesis Aspergillus fumigatus has various secondary metabolites such as *fumagillin*, *fumitoxins, fumigaclavines* A & C, *fumitremorgins, gliotoxin, trypacidin*, *pseurotins, asam helvolat, pyripyropens, metil-sulochrin, verruculogen,* and *fumiquinazoline*s. Some of these metabolites, such as gliotoxins, are involved in damaging the immune system host, causing serious health hazards.[14]

Species *Aspergillus sp* is a unique pathogen that infects humans. This pathogen is capable of causing invasive disease and allergies. When inhalation occurs, alveolar macrophage conidia in normal human lungs will kill the pathogen quickly. In damaged lungs, colonization of the respiratory tract can occur, which may be temporary or semi-permanent. Impaired mucociliary clearance is the main damage that occurs in the lung cavity due to damage from previous lung disease and in bronchi that experience ectasis, as explained in Figure 2. Phagocyte dysfunction is a common cause of invasive aspergillosis, including subacute cases such as AIDS or chronic granulomatous disease.[19]

Lung cancer can cause damage to the mucociliary and respiratory tract epithelium. The airway epithelium makes a significant contribution to the protective function of the airway. mucociliary movement, intercellular apical junctional complexes regulating paracellular permeability, and antimicrobial peptides secreted by airway epithelial cells are the three main components of airway protective function. Mucociliary clearance is an innate lung defense mechanism driven primarily by ciliated cells. Respiratory mucus traps pathogens entering the airways, and pulmonary cilia push them out through coordinated, directional movements.[7]

These three components work together to clear pathogens, allergens, and inhaled particles. Therefore, impairment of one or more important components of this barrier function may increase susceptibility to infection.[7] Airway obstruction due to malignancy may be caused by extrinsic compression by the tumor or enlarged lymph nodes, endobronchial obstruction from an intraluminal mass, or a combination of both. Smaller airways can be obstructed by the spread of lymphangitic malignancies. These mechanisms have in common the stasis of secretions in the bronchi and alveoli distal to the obstruction, the formation of atelectasis, and microbial colonization and infection. The infection that occurs can cause extensive local damage to the lung parenchyma.[20]

The physical barrier of the respiratory tract is the first line of defense against inhaled *Aspergillus sp* conidia, after which the respiratory epithelium is the first point of contact with inhaled conidia.[21,22] The airway epithelium plays a role in fungal clearance and the production of cytokines and antimicrobial peptides.[23-25] Conidia can escape the respiratory epithelium and are then challenged by cells of the innate immune system, including pulmonary alveolar macrophages and dendritic cells.[26] Bronchial obstruction is more common in squamous cell and small cell carcinomas than in adenocarcinoma and large cell carcinoma. Infection develops in the distal part of the obstruction, resulting in damage to the lung parenchyma and the formation of cavities in the lung.[20]

Tumor invasion of the vagus nerve or recurrent laryngeal nerve can cause glottic incompetence and ciliary dysfunction, thereby increasing the possibility of aspiration and fungal colonization. Aspiration after swallowing can also occur due to food residue that cannot be cleaned on the paralyzed side. Treatment modality is a risk factor for infectious complications in lung cancer patients. Radiotherapy causes various toxicities, including pneumonitis, esophagitis, and other types of mucosal trauma, which are predisposing factors for infection. Patients receiving chemotherapy are also at increased risk of neutropenia, especially if myelosuppressive agents are used.[21] In lung cancer patients, neutropenia and lymphopenia occur after radiotherapy and chemotherapy treatment.[21]

Research conducted by Sarihan et al. found that radiation-induced lymphopenia was associated with an increased risk of infection in the first 3 months after radiation therapy. Low lymphocyte counts correlate with higher levels of inflammation response dysregulation in the host, which can cause an inflammatory state. In patients with a diagnosis, human immunodeficiency virus (HIV) decreases, and damage to lymphocytes results in infection.[21] Lymphopenia with a lymphocyte count <1100 cells/mL is associated with an increased risk of hospital admission with infection and an increased risk of death. Lymphopenia with a lymphocyte cell count ≤1500 cells/mL is associated with reduced survival. In cancer patients, lymphocytes <100 cells/mL are associated with a risk of death with microbiologically confirmed sepsis.[21] Neutrophil count <1000 cells/mL causes an increased risk of infection in lung cancer patients. One of the most studied immunological markers in lung cancer patients is the CD4, CD8, and CD4/CD8 ratio.[21] The reduced number of CD4 cells, quantitative changes in lymphocytes, and the existence of other theories stating that T cell dysfunction occurs in lung cancer cause individuals with lung cancer to become immunocompromised so it is easy for infections to occur, including fungal

infections, which can make healing difficult.[22] Chemotherapy-induced neutropenia (CIN) is one of the most commonly reported side effects in cancer patients.[22] Chemotherapy-induced neutropenia is a toxicity that causes a delay in treatment and/or a reduction in chemotherapy dose.[22] Chemotherapy agents act in the bone marrow when active cell division occurs and suppress hematopoietic stem cells, causing a decrease in the absolute number of neutrophils in the blood circulation. Triplet/doublet regimens increased the incidence of CIN and myelotoxicity than single chemotherapy agent regimens. A retrospective comparative study by Gargiulo et al. regarding the toxicity of several chemotherapeutic agents concluded that neutropenia was frequently observed in the chemotherapeutic drugs paclitaxel (18%), carboplatin and paclitaxel (23%), oxaliplatin and fluorouracil and leucovorin (23%).[22]

Chemotherapy in cases of malignancy can generally cause immunosuppression and induce anergy or immunoparalysis.[2] Patients with lung malignancies can experience recurrent fevers due to post-obstruction pneumonia, as well as other lung abnormalities in the form of cavities or lung nodules. Administration of chemotherapy and high doses of corticosteroids is associated with increased pulmonary aspergillosis in malignant patients. The use of high doses of corticosteroids can disrupt natural killer (NK) cell function, suppress the production of pro-inflammatory cytokines and chemokines, and interfere with the differentiation and activation of dendritic cells.[2]

Tumors can produce activating growth factors, cytokines, and chemokines myeloid-derived suppressor cells (MDSC). MDSCs can suppress immune responses to tumor antigens and accelerate tumor progression and tumor metastasis. There are several mechanisms by which MDSCs can suppress antitumor responses, including MDSCs inhibiting T cell function in tumor tissue. MDSCs were first identified as immunosuppressive myeloid cells in lung cancer patients. MDSCs have a strong ability to suppress various functions of T cells. Tumor-associated macrophages or neutrophils produce hydrogen peroxide (H_2O_2), which substantially reduces T cell proliferation. Reactive oxygen species are physiologically produced by activated neutrophils and macrophages as mediators of innate immunity.[2] In chronic inflammation, ROS can weaken T cell responses by affecting CD3-ζ expression.[9,24]

ROS can also influence affinity antigen-receptor cell T (Ag-TCR) specificity, which may explain the specificity of MDSC-induced tolerance. The effects of ROS and MDSC can affect CD8 T cells through the inhibitory molecules B7-H1 and B7-H4. MDSCs can improve immunosuppression by directly inducing regulatory T cells (Treg) through the production of interleukin (IL-10) and transforming growth factor (TGF-β). Tregs actively regulate the activity and reactions of antitumor T cells and NK cells. Cysteine, which is an essential amino acid for T-cell activation, is also difficult to find because of MDSC.[9,24]

A study conducted by Thomas et al. showed that the level of ripening dendritic cells (DC) in patients with lung tumors is significantly lower than in healthy people. A dendritic cell is critical for the activation of antigen-specific CD8 T lymphocytes, a critical step in the initiation of innate and adaptive immune responses that are essential for the clearance of infections and tumors. Research conducted by Pyfferoin et al. also explains that the DC subset that can activate CD8 T cells is reduced in number in lung cancer patients. This study shows that lung cancer dynamically removes functional DCs from tumor regions to support malignant progression.[26] Shi et al. use flow cytometry to examine pDCs in the peripheral blood of 52 NSCLC patients and 52 healthy controls.[26]

Patients with higher tumor stages had higher pDC levels than those with lower tumor stages. Rosalinda Sorrentino et al. isolated pDCs from NSCLC tissue and found that a higher percentage of immunosuppressive-phenotype pDCs in lung tumor areas with high expression of cell membrane receptors and PD-L1 contributed to an immunosuppressive tumor microenvironment. Reducing the number of

pDCs can, in many cases, improve the immunosuppressive environment. Tumor-associated pDCs show impaired type I interferon (IFN) production. These IFNs have been shown to play important roles in cytotoxic, immunosuppressive, and anti-tumor responses.[27] Intratumoral activation of pDCs by agonists Toll-Like Receptors (TLR-9) and activation of TLR-9 in the lung leads to the recruitment of regulatory T cells, thereby contributing to immunosuppression.[27]

The mechanism of immunosuppression by regDCs has been tested in various studies. Spallanzani et al. demonstrated that regDCs suppress IFN-γ secretion by NK cells through reduction of IL-18 secretion and by an active cell-to-cell mechanism mediated by IL-10. This mechanism can produce an immunosuppressive state. Zhang et al. showed that regDCs can induce higher-performance Tregs to maintain immune tolerance, thereby causing a state of immunosuppression.[28] Unequal differentiation of DC precursors in tumor microenvironment (TME) has been demonstrated in many studies.[28]

After culturing DCs in a medium with serum from lung tumor patients, the expression of the molecule co-stimulator, like a cluster of differentiation (CD)40, CD80, CD86, major histocompatibility complex (MHC) type II, and IL-12 are disrupted. These DCs are also unable to present antigens to activate T-cell responses. The lactic acid in the TME inhibits TLR3 and the stimulator of the IFN signaling gene (STING), thereby inhibiting the secretion of IL-12 and IFN-I by DCs. Overexpression of B7-H3 in lung cancer tissue can suppress T-cell stimulation.[29] Aspergillosis is most likely related to immune or pulmonary defense disorders such as mannose-binding lectin deficiency or immune dysregulation, such as the predominance of the T helper 2 (Th2) cell axis.[20]

Aspergillus is a fungus that can cause various clinical syndromes. Despite exposure to conidia *Aspergillus sp* via inhalation being common, only a small proportion of those exposed will develop pulmonary disease. Clinical picture, course, and prognosis of infection Aspergillus really depends on the level of immunity of the person's host, despite increasing knowledge of genetic disorders. Interactions between immune dysfunction, pathogens, and host or hyperreactivity determine which clinical syndrome is more likely to develop, as described in Figure 3.[21]

The classic risk factor for invasive pulmonary aspergillosis is neutropenia, and the likelihood of IPA correlates with the duration and severity of neutropenia. Platelets are also important in defense against IPA, and thrombocytopenia tends to go hand in hand with neutropenia. Angioinvasion is involved in the pathogenesis of host neutropenia and is a response to higher spread to other organs such as the skin, brain, or eyes. Patients who have a higher risk for IPA are patients who have allo-hematopoietic stem cell transplantation (HSCT) genetics and patients with long-term neutropenia after chemotherapy.

Invasive pulmonary aspergillosis in patients with neutropenia has been reviewed extensively.[21] IPA also occurs in patients who do not experience neutropenia. The most common risk factor is the use of corticosteroids before hospital admission.[21] Invasive pulmonary aspergillosis occurs in patients receiving solid organ transplants (especially lung and heart), patients with acquired immune deficiency syndrome (AIDS), chronic obstructive pulmonary disease (COPD), intensive care unit patients, critically ill patients, patients with liver failure and patients with chronic granulomatous disease. Angioinvasion is not a common feature in patients who do not experience neutropenia. This is different from neutropenic patients.[21]

Many cases work relatively well slowly, and the condition continues for weeks. Lack of angioinvasion on imaging is associated with a more protracted clinical course, such as explained in Figure 4, and delayed diagnosis in heart transplant recipients. As a result, the diagnosis is often not considered because the symptoms and imaging results are non-specific.[21] Conidia that escape from macrophages are eliminated by recruiting neutrophils and monocytes. Neutrophil extracellular traps (NET) contribute to the defense of

host innate, and neutrophils exert a wide variety of antifungal effector functions, including recognition, phagocytosis, intracellular clearance mediated by oxidative mechanisms and non-oxidative, secretion of antimicrobial molecules, and release of NETs. Failure to prevent conidia germination results in hyphal growth tissue invasion and marks the initiation of fungal disease.[27]

Innate immune cells express pattern recognition receptors (PRR) that recognize pathogen-associated molecular patterns (PAMPs) in fungi and activate effector functions, including phagocytosis and the production of proinflammatory cytokines and chemokines that regulate innate and adaptive immunity.[14] Incomplete elimination occurs in individuals who are immunocompromised. Inhaled fungal conidia cause germination and tissue invasion by fungal hyphae.[1] Severe and long-term neutropenia and monocytopenia and effects regimen chemotherapy *myelotoxic* and hematopoietic cell transplantation are predisposing factors to infection Aspergillus sp. Severe pharmacological disruption of myeloid cell function, for example, by long-term exposure to corticosteroids, predisposes patients to infection with *Aspergillus sp.*[14]

Inhaled conidia of *Aspergillus fumigatus* cause early recognition of infection by pulmonary epithelial cells and innate cells, including alveolar macrophages and dendritic cells. This immediate response results in the production of chemokines that promote the rapid recruitment of neutrophils, followed by the subsequent arrival of monocytes, DCs, mast cells, eosinophils, and NK cells. All of these innate cells work together in the elimination of fungal conidia by producing a combination of cytokines and protective factors in the form of ROS, NET, tumor necrosis factor (TNF), IFN, dendritic cells, and plasmacytoid dendritic cells.[28] Simultaneous disruption of the patient's innate immune system, e.g., chemotherapy myelotoxic, corticosteroids, and myeloid function inhibitors, a high risk of *Aspergillus sp* infection.[14]

The main T-helper derivatives, Th1, Th2, and Th17, were shown to play an important role in aspergillosis.[29] A dominant Th1 response is required for resistance to aspergillosis and induction of efficient antifungal responses.[30] Protection mediated by the Th1 subset correlates with the production of the cytokine IFNγ that activates the potential fungicidal activity of innate immune cells. Th2 responses characterized by the production of IL-4, IL-5, IL-13, and IL-10 mediate anti-inflammatory responses, allergies, and fungal persistence in the lung. Response Strong Th2 is associated with severe aspergillosis infection, and this response counteracts the protective Th1 response mediated by the cytokine IL-4.[30] The hallmark of Th17 cells is the production of IL-17A and IL-17F, which triggers the recruitment and activation of neutrophils to the site of infection and induces the pro-inflammatory cytokines IL-6, IL-1β, G-CSF and TNFα as well as the chemokines CXCL8, MIP-1 and MCP1. Potentiation of neutrophils by IL-17A increases the production of ROS, proteolytic enzymes, and antimicrobial peptides, which all aim to eliminate the fungus. T helper 17 has an important role in cleaning mold. Uncontrolled or prolonged Th17 activation is detrimental to the host because it causes lung damage and persistent inflammation. Enhanced Th17 response is associated with severe immunopathology characterized by massive neutrophil infiltrates in the lung parenchyma and impaired fungal clearance.[30] Epithelial cells, dendritic cells, and alveolar macrophages constitute the innate immune response to *A. fumigatus*. PRR engagement in these cells triggers the pathway transduction, leading to the production of different lineage-polarizing cytokines. Antigen presentation via MHC-II and molecular binding co-stimulator, in turn, causes activation and differentiation of naïve CD4 T-helper cells into different effector lineages: Th1, Th17, Th22, Th2, Th9, Treg, and Tr1 as described in figure 6. These effector cells differentially contribute to protection against infection fungi, adverse immunopathology, or in the setting of adaptive immune responses.[30]

Clinical manifestations

There are three major categories of pulmonary aspergillosis, namely allergic bronchopulmonary

aspergillosis (ABPA), chronic pulmonary aspergillosis, and invasive pulmonary aspergillosis. Categories depend on characteristics of host underlying conditions and interactions between the fungus and its host, such as explained in Figure 7. The widespread use of chemotherapeutic and immunosuppressive agents results in overlap between these categories. Pulmonary aspergillosis is often described as a semi-continuous allergic disease, noninvasive and invasive.[12] Invasive pulmonary aspergillosis is a severe clinical manifestation of aspergillosis and can be found not only in patients with severe immune system disorders but also in critically ill patients with COPD. Aspergilloma and ABPA are forms of invasiveness of aspergillosis. Aspergilloma is a fungal ball that develops in a pre-existing cavity in the lung parenchyma, while ABPA is a manifestation of hypersensitivity in the lungs that almost always attacks asthmatic patients or cystic fibrosis.[31] CPA is a fungal disease that usually occurs in immunocompetent or mildly immunosuppressed patients with underlying respiratory disorders. CPA is an important and often overlooked fungal infection.[10] The clinical spectrum of CPA is outlined in the figure below.

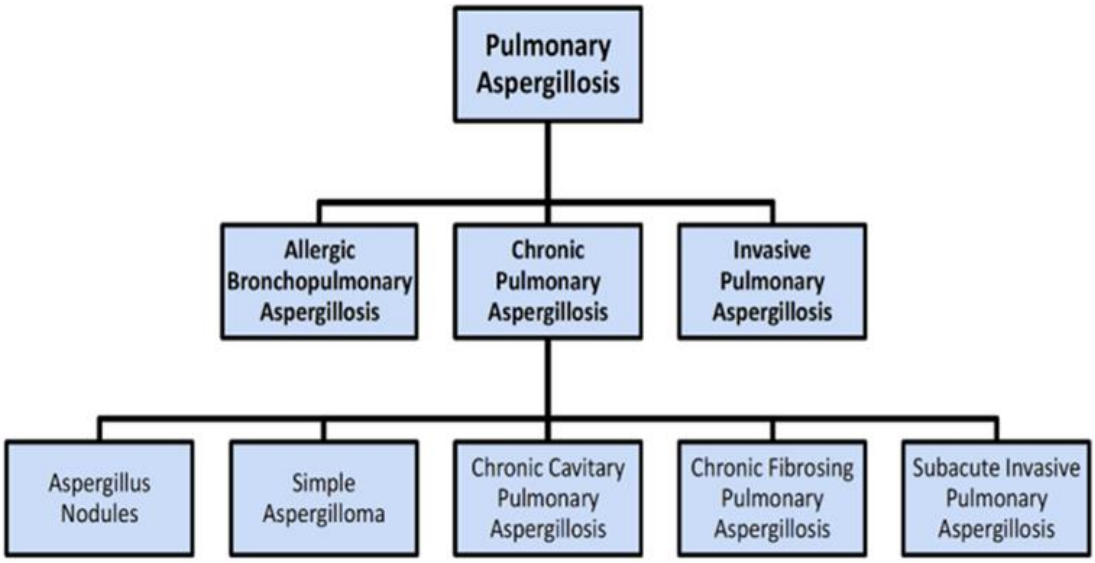

Figure 1. Clinical spectrum chronic pulmonary aspergillosis.

Treatment

Prophylactic therapy is the administration of anti-fungal drugs (OAJ) to patients who have risk factors without signs of infection with the aim of preventing the emergence of fungal infections. Prophylactic therapy is given early in the period of high risk of infection. Empirical therapy is the administration of OAJ to patients who have risk factors accompanied by signs of infection, for example, persistent fever with neutropenia usually for 4-7 days, whose etiology is unknown and does not improve after adequate antibiotic therapy for 3-7 days. Empirical therapy is given to patients with a diagnosis possible. Therapy pre-emptive (targeted prophylaxis) is the administration of OAJ to patients who have risk factors, accompanied by clinical symptoms and radiological and/or laboratory examination results that are suspicious of fungal infection. Pre-emptive therapy is given to patients with a probable diagnosis.

Voriconazole (A) is highly recommended as primary therapy for invasive pulmonary aspergillosis. Other antifungals such as amphotericin B (B), caspofungin (B), micafungin (B), posaconazole (B), and itraconazole (B) are alternative therapies. In patients receiving long-term immunosuppressive therapy, antifungal therapy should be continued (B). Prevention of recurrent infections by continuing antifungal therapy in patients successfully treated for past invasive aspergillosis with risk of neutropenia (B). Discontinuation/reduction of corticosteroid dose is recommended for patients with invasive pulmonary aspergillosis (C).[32-36] Rapid initiation of therapy in IPA reduces mortality and is important for preventing disease progression. Empiric IPA therapy in patients receiving induction chemotherapy is also associated with better survival rates. Voriconazole remains the initial drug of choice in treatment, administered in two intravenous doses of 6 mg/kg on day 1, followed by 4 mg/kg every 12 hours. Switching to an oral formulation may be considered in patients who show signs of improvement and who can tolerate oral therapy. Voriconazole is generally well tolerated. Side effects of variconazole are blurred, photophobia, and altered color discrimination.[12]

Itraconazole is administered at a dose of 200 mg twice daily for at least six months and requires frequent monitoring of drug levels, given its narrow therapeutic range and considerable toxicity.[12] Other oral azoles, such as voriconazole and posaconazole, also appear effective in disease remission and can be used as a second or third line after itraconazole. Nebulized amphotericin B (NEB), given for four months in stable patients with recurrent exacerbations of ABPA, resulted in a significant reduction in the number of exacerbations at one year. Omalizumab, a recombinant anti-IgE monoclonal antibody, is a promising glucocorticoid-sparing agent, especially in patients who cannot tolerate antifungal therapy.[12] A minimum of 6-12 weeks of antifungal treatment is recommended. Often, patients require therapy for several months to more than a year. Surgical resection has a limited role in the treatment of IPA but is effective in patients with IPA and massive hemoptysis or refractory disease. Wedge resection and lobectomy without significant loss of lung function are preferable to pneumonectomy. IDSA guidelines support prophylaxis during prolonged neutropenia and immunosuppression. Strong recommendations for the use of posaconazole or voriconazole for prophylaxis come from large randomized clinical trials demonstrating its superiority over other triazoles. Itraconazole, micafungin, and caspofungin may also be effective.[12] A summary of treatment for pulmonary aspergillosis can be seen in Table 1.

Prognosis

Invasive pulmonary aspergillosis in lung cancer can result in a high mortality rate, reaching 50-100%.[2] Cancer treatment in the form of chemotherapy and radiotherapy can cause lymphopenia and neutropenia. Lymphopenia with a lymphocyte count <1100 cells/mL is associated with an increased risk of hospital admission with infection and an increased risk of death. Lymphopenia with a lymphocyte cell count ≤1500 cells/mL is associated with reduced survival. In cancer patients, lymphocytes <100 cells/mL are associated with a risk of death with microbiologically confirmed sepsis.[21] Neutrophil count <1000 cells/mL causes an increased risk of infection in lung cancer patients. Chemotherapy-induced neutropenia is a toxicity that causes a delay in treatment and/or a reduction in chemotherapy dose.[22] when the absolute neutrophil count is less than 500 cells/mm^3, the mortality rate exceeds 50%.[3] Clinical picture, course, and prognosis of infection Aspergillus sp really depend on the level of immunity of the host. Neutropenic patients will have more severe symptoms, and infection can spread through angioinvasion.[12]

Table 1. Treatment of pulmonary aspergillosis.

Disease manifestations	Care recommendations	Information
Aspergillosis invasive	Primary therapy: Intravenous voriconazole (6 mg/kg every 12 hours for 1 day, followed by 4 mg/kg every 12 hours) until improvement, followed by oral voriconazole (200 mg every 12 hours) or itraconazole orally (400-600 mg/day) until resolution or stabilization of all clinical and radiographic manifestations OR Intravenous liposomal amphotericin B (3–5 mg/kg/day) until improvement, followed by oral voriconazole (200 mg every 12 hours) or oral itraconazole (400-600 mg/day) until resolution or stabilization of all clinical and radiographic manifestations Rescue therapy: intravenous caspofungin (70 mg Day 1 and 50 mg/day intravenously thereafter) or intravenous micafungin (100-150 mg/day) until improvement, followed by oral voriconazole (200 mg every 12 hours) or oral itraconazole (400-600 mg/day) until resolution of the disease OR Posaconazole (200 mg four times a day initially, then 400 mg twice) daily orally after disease stabilization	Follow-up serum galactomannan levels Improved immune system suppression (neutropenia)
Chronic necrotizing (''semi-invasive'') pulmonary aspergillosis	For mild to moderate disease, voriconazole (200 mg every 12 hours) or itraconazole (400-600 mg/day) until resolution or stabilization of all clinical and radiographic manifestations. If clinically severe, consider starting with intravenous liposomal amphotericin B or voriconazole as described above for invasive disease. Consider surgical resection	Improved immunosuppression (corticosteroids) Get rid of the spread.
Bronchopulmonary allergy aspergillosis	Corticosteroids (dose and duration vary widely, with dosage adjusted accordingly on the degree of airflow obstruction, eosinophilia, and IgE levels)	Itraconazole (200 mg twice daily for 16 weeks initially) has been used as a steroid-sparing agent
Aspergilloma	There is no indication of antifungal agents Embolization and bronchial angiography surgical resection	It can become a progressive chronic lung disease or invasive if immunosuppressed
Hypersensitivity pneumonitis	There is no indication of antifungal agents Corticosteroids	Avoidance measures

2. Conclusion

Diagnosis of aspergillosis is difficult to establish because the symptoms are non-specific, based on clinical, radiological, and microbiological criteria, and exclude other more frequent causes of the symptoms reported. Lung cancer patients are at high risk for infection aspergillosis lungs, especially patients who have received treatment in the form of chemotherapy or radiotherapy, which can cause neutropenia and lymphopenia, as well as high-dose and long-term steroid treatment. CIN can cause treatment delays/reduction of chemotherapy doses.

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