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Review Article

Tuberculosis Co-Infection in Lung Cancer

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Abstract

Lung cancer and tuberculosis are two diseases with large numbers of cases and high mortality rates. Pulmonary tuberculosis is an infection in the lungs caused by the bacterium Mycobacterium tuberculosis. Pulmonary tuberculosis and lung cancer often present with similar clinical symptoms, and there is often a delay in diagnosis. Tuberculosis co-infection in lung cancer patients is found to be approximately 2. Several studies have shown a positive correlation between pulmonary tuberculosis and lung cancer. A person with a history of tuberculosis has a 1.7-2 times greater risk of developing lung cancer. Co-infection of tuberculosis and lung cancer can occur sequentially or simultaneously. The mechanism of lung cancer with a history of tuberculosis is due to chronic inflammation, scarring or epidermal growth factor receptor (EGFR) mutation. While comorbid tuberculosis in lung cancer may occur with two mechanisms, due to tumorigenesis caused by tuberculosis or tuberculosis induced cancer. Proper and rapid diagnosis of comorbid tuberculosis in lung cancer is a challenge so that patients receive appropriate treatment.

Keywords: *co-infection, lung cancer, tuberculosis*

Abstrak

Kanker paru dan tuberkulosis merupakan dua penyakit dengan jumlah kasus yang besar serta angka mortalitas yang tinggi. Tuberkulosis paru adalah infeksi pada paru yang disebabkan oleh bakteri *Mycobacterium tuberculosis*. Tuberkulosis paru dan kanker paru sering kali menunjukkan gejala klinis yang serupa, sehingga kerap terjadi keterlambatan diagnosis. Ko-infeksi tuberkulosis pada pasien kanker paru ditemukan sekitar 2%. Beberapa studi menunjukkan adanya korelasi positif antara tuberkulosis paru dan kanker paru. Seseorang dengan riwayat tuberkulosis memiliki risiko 1,7–2 kali lebih tinggi untuk mengalami kanker paru. Ko-infeksi tuberkulosis dan kanker paru dapat terjadi secara berurutan maupun simultan. Mekanisme terjadinya kanker paru pada pasien dengan riwayat tuberkulosis diduga berkaitan dengan inflamasi kronis, jaringan parut (scarring), atau mutasi *epidermal growth factor receptor* (EGFR). Sementara itu, tuberkulosis sebagai komorbid pada kanker paru dapat terjadi melalui dua mekanisme, yaitu akibat proses tumorigenesis yang dipicu oleh tuberkulosis atau kanker yang menginduksi terjadinya tuberkulosis. Diagnosis yang tepat dan cepat terhadap komorbid tuberkulosis pada kanker paru masih menjadi tantangan, agar pasien dapat memperoleh terapi yang sesuai.

Kata kunci: *kanker paru, ko-infeksi, tuberkulosis*

Background

Lung cancer is the leading cause of cancer death and is estimated to have 2.2 million new cases with 1.8 million deaths by 2020.[1,2] Tuberculosis (TB) is the leading cause of death from infection in the world, with an estimated 1.3 million deaths by 2022.[3] It is known that TB increases the risk of lung cancer and affects its prognosis.[4] Patients with lung cancer and TB will have a higher mortality compared to those without TB.[5] Coexistence of TB and lung cancer is rare but can occur with an incidence of coexistence of about 2%.[6] From several studies, the risk of lung cancer increases 1.7-2 times in people with a history of tuberculosis.[7]

There is some evidence that TB can coexist with cancer, where TB is a susceptibility factor for cancer and cancer can increase the risk of TB incidence.[8] The mechanism of copathogenesis remains unclear, but it is thought to be primarily due to chronic inflammation of the lung, in cases of lung cancer with prior TB.[9] Long-term TB creates long-standing scarring that leads to lung epithelial metaplasia.[10] Another mechanism of coexistence is tumorigenesis due to tuberculosis or cancer-induced tuberculosis.[8] The clinical symptoms of TB are very similar to those of lung cancer, hence the need for caution and care when diagnosing patients with symptoms of TB or lung cancer. Diagnosis and treatment of the coexistence of pulmonary TB and lung cancer remains a challenge in TB-endemic countries. Early detection is needed before the disease reaches an advanced stage.[11]

Content

Tuberculosis

Pulmonary tuberculosis is a lung infection caused by the bacterium Mycobacterium tuberculosis. Tuberculosis is a significant public health problem in Indonesia, with a high prevalence rate. In 2022, Indonesia reported an estimated 10.6 million new TB cases, ranking second globally after India.[12] The incidence of pulmonary tuberculosis in Indonesia (10%) is second only to India (27%).[3] In 2021, the incidence rate of TB in Indonesia was 354 per 100,000 population with a TB mortality rate of 52 per 100,000 population.[13] The prevalence of pulmonary TB in Indonesia in the population aged 15 years and over is approximately 759 cases per 100,000 population.[14]

Lung Cancer

Lung cancer is a serious disease that affects 2.4 million people in 2022 (12.4% of all cancers), killing 1.8 million people, approximately 18.7% of all cancer deaths in the world.[15] In 2018, lung cancer was the leading cause of cancer death in Indonesia, accounting for approximately 12.6% of all cancer deaths and 8.6% of all incidents. The total number of cases per year is expected to almost double from 30,023 in 2018 to 54,983 cases in 2040.[16] This type of cancer has a poor prognosis and poor clinical outcomes, mainly due to late diagnosis, ineffective treatment, and tumor cell resistance. There are currently about 2.09 million of lung cancer and 1.76 million deaths each year.[17]

Co-infection with tuberculosis and lung cancer

A study found that 7.3% of lung cancer patients in Indonesia had a history of tuberculosis (TB).18 Coexistence of TB and lung cancer complicates diagnosis and worsens prognosis due to similar clinical and radiologic features.18) Patients diagnosed with lung cancer along with pulmonary tuberculosis have a higher mortality rate compared to lung cancer patients without TB.[5] Coexistence of TB and lung cancer is rarely described in the literature, but the incidence of coexistence is about 2%[6,19], as found by Cicėnas et al, about 2.1% of lung cancer patients are diagnosed with pulmonary tuberculosis.[19]

Co-infection with tuberculosis (TB) and lung cancer are two diseases that occur simultaneously or sequentially in the same individual. Co-infection is divided into two, simultaneous or sequential. Simultaneous is when both tuberculosis and lung cancer are diagnosed simultaneously, usually within a short period of time (less than two months). Sequential is where one condition precedes the other, with patients diagnosed with tuberculosis first and then lung cancer or lung cancer and then lung tuberculosis. [20-21]

Correlation of tuberculosis and lung cancer

Several studies have shown a positive correlation between tuberculosis incidence and lung cancer, Tuberculosis patients have a 50% greater chance of developing lung cancer. Those with a history of tuberculosis for more than 20 years are 2.5 times more likely develop cancer.[22] It is reported that the risk of lung cancer increases 1.7-fold in people with TB.[7] A cohort study also found that the incidence of lung cancer in TB patients was 269 per 100,000 people per year, which is higher than in the normal population (153 per 100,000 people per year).[4]

A large body of epidemiologic data has shown that pulmonary TB is closely associated with lung cancer (shown in Table 1).[23]

Table 1. Epidemiologic Data of Pulmonary TB and Lung Cancer

Researcher (Year)	Cohort size (Number of Controls)	Methods	Results	Conclusion
Leung (2020)	52,480 cancer cases	Meta-analysis	Lung cancer RR 1.7 (95% CI: 1.5-2.0) against TB	TB is linked to lung cancer.
Everatt (2016)	21,986 TB patients	Retrospective study	477 TB patients developed lung cancer, a 3.5 times increased risk of cancer lung in subjects with a history of TB.	The increased risk of lung cancer in the TB cohort is associated with many factors.
Oh (2020)	2,640 patients with pre-existing TB, 17,612 controls	Retrospective cohort study	HR of lung cancer 3.2 (95% CI: 1.9-5.6) in patients with pulmonary TB.	A higher risk of lung cancer was found in patients with a previous history of TB.
Wu (2011)	5,657 pre-existing TB patients, 23,984 controls	Retrospective cohort study	Lung cancer IRR 1.8 (95% CI: 1.3-2.3) in patients with pulmonary TB.	Pulmonary TB is associated with an increased risk of lung cancer.
Yu (2011)	4,480 TB patients, 712.392 control	Prospective longitudinal study	The incidence of lung cancer in TB patients is almost 11 times higher than in controls (26.3 vs. 2.4 /10,000) people/year	TB patients have an increased risk of lung cancer.
Zheng (1987)	1,405 lung cancer patients, 1,495 controls	Prospective longitudinal study	The OR of lung cancer was 1.5 in the TB cohort and remained 2.5 times higher after TB diagnosis in the last 20 years.	TB may predispose to lung cancer
Shiels (2011)	1,403 male smokers with TB, 28,860 male non-smokers with TB	Prospective longitudinal study	HR of lung cancer 2 in TB patients (95% CI: 1.5- 2.7), and the risk of lung cancer was highest around 2 years after TB diagnosis (HR: 5.0: 95% CI: 3.0-8.5), but the risk remained elevated at longer latencies (HR: 1.5; 95% CI:1.1-2.2).	TB is associated with an increased risk of lung cancer in male smokers.
Liang (2009)	19,143 TB cases, 118.191 controls	Meta-analysis	Lung cancer RR 1.7 in patients with TB and passive smoking or exposure to environmental smoke (RR 1.8; 95% confidence interval (95% CI: 1.4-2.2 and 2.9; 95% CI: 1.6-5.3).	TB has a direct association with lung cancer, especially adenocarcinoma.
Brenner (2011)	30 studies, 82,716 cases	Meta-analysis	The RR of lung cancer was 1.8 (95% CI: 1.5-2.1) in patients with previous TB.	Pulmonary TB is associated with an increased risk of lung cancer.

Note:TB: *Tuberculosis*; HR : *Hazard Ratio*; CI: *Confidence Interval*; IRR: *Incidence Rate Ratio*; OR: *Odds Ratio*, RR: *Relative Risk*; LTBI: *Latent Tuberculosis Infection*

Source: Xiong K, Sun W, He Y, Fan L. Advances in molecular mechanisms of interaction between Mycobacterium tuberculosis and lung cancer: A narrative review. Vol. 10, Translational Lung Cancer Research. AME Publishing Company; 2021. p. 4012-26.

Everatt et al found out of 21,986 pulmonary TB patients in Lithuania, 477 TB patients developed lung cancer and patients with a history of TB had a 3.5 times higher risk of lung cancer.[24] Liang et al conducted a systematic review and meta- analysis of 37

case-control studies and 4 cohort studies to assess the association between lung cancer risk and pre-existing tuberculosis.[7] The results showed pre- existing TB significantly increased the risk of lung cancer [(RR): 1.7; 95% confidence interval (CI): 1,5-2,0). The increase in cancer risk was 2-fold until more than two decades after TB was diagnosed.[7] Brenner et al conducted a meta- analysis of 30 studies, a significantly increased risk of lung cancer was found in patients with a history of TB compared to those without TB (RR: 1.8; 95% CI: 0.5-2.1).[25] Leung et al covering 52,480 cancer cases showed tuberculosis associated lung cancer.[26]

A retrospective cohort study in China showed that lung cancer mortality was higher in patients with a history of TB (25 per 1,000 person-years) than without lung TB (3.1 per 1,000 person-years) in the first 5 years HR ranged from 6.7 to 13), at 5-9.9 years (HR: 3,4; 95% CI: 1.3-9.1), or at ≥10 years (HR: 3.0; 95% CI: 1.3-7.3).27 Based on research conducted by Heuvers et al showed that 13 of 214 lung cancer patients had a history of pulmonary tuberculosis, and the survival of lung cancer patients with previous pulmonary TB was significantly shorter (HR: 2.4, 95% CI: 1.1-4.9) with a difference of± 311 days.[28] So from some of these studies it can be said that a history of pulmonary tuberculosis increases the risk of lung cancer and increases the mortality rate of patients.

Pathophysiology of Tuberculosis

Mycobacterium tuberculosis (Mtb) is a large nonmotile rod-shaped obligate aerobic bacterium that requires oxygen to. Mtb is an intracellular pathogen capable of infecting human mononuclear phagocytes, spending most of its life cycle in macrophages.[29] Following transmission of Mtb to a new host via inhalation, the bacilli enter the lung and are digested by macrophages. Further immune cells are recruited to fortify the infected macrophages, leading to granuloma formation. Healthy individuals remain latently infected, and infection can be prevented at this stage, but are susceptible to the risk of reactivation (Figure 1).[30]

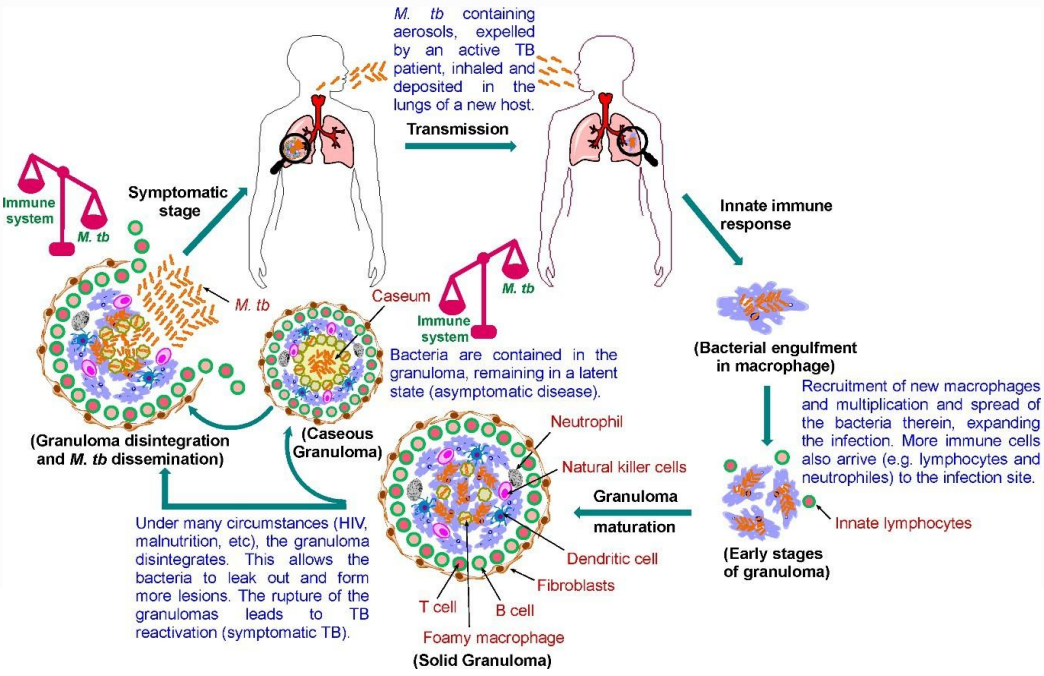

Figure 1. Pathophysiology of Pulmonary TB[30]

Foamy macrophages release their lipid content during necrosis, causing caseation (cheese-like structure). Caseum is the decay that occurs at the core of the granuloma that disrupts its rigid integrity. As the granuloma develops, bacilli begin to seep out of the macrophages into caseum layer. When reactivation occurs, Mtb proliferates and the bacterial count becomes so high, that the granuloma ruptures, spreading the bacteria into the airways. The bacilli are then expelled as infectious aerosolized droplets, restarting the cycle, and infecting others. [30]

Sequential Tuberculosis - Lung Cancer Co-Infection

Many studies have documented an association between TB and lung cancer (Table 1), but the mechanism remains unclear. It is difficult to identify a causal relationship between lung cancer and TB. The following are some possible mechanisms in the co-infection of lung cancer with a previous history of tuberculosis in patients, including due to chronic inflammation, Epidermal Growth Receptor EGFR gene mutation and scarring.[23,30]

a. Chronic inflammation
In the early phase of Mtb infection, bacilli are phagocytosed by alveolar macrophages (AM). These cells are then activated and adopt a pro-inflammatory phenotype, recruiting many immune cells to the infection site, including interstitial macrophages (IM). This decreases oxidative phosphorylation with energy from AM.[31] This type of energy gain is driven by fatty acid oxidation, making the environment more conducive for myco-bacterial infection.[32] IM also increases aerobic glycolysis, as in the Warburg effect, providing biosynthetic precursors necessary for rapid cell growth and proliferation.[33] This mechanism is part of the effort to eliminate infection, so if aerobic glycolysis is inhibited at this stage, the resulting immunological changes lead to increased Mtb survival, mainly due to decreased levels of pro-inflammatory IL-1β.[34]

Inflammatory cells produce many cytokines and chemokines that form an attractive environment for tumor progression, promoting the formation of new blood vessels from existing ones, in addition to facilitating genomic instability.[35] In chronic inflammation, by producing ROS and RNS, most phagocytic cells induce DNA damage in proliferating cells due to the resulting peroxynitrite production. If DNA damage occurs continuously and repeatedly, it may result in permanent genomic changes, such as mutations, deletions or rearrangements (Figure 2).[33-35]

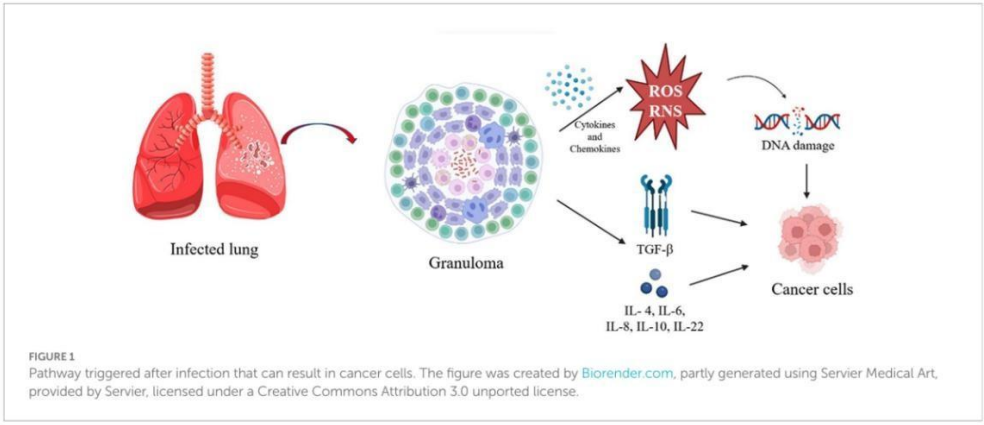

Figure 2. Pathways Triggered After Infection That Can Lead to Cancer Cells[30]

Lung cancer originating from chronic uncontrolled inflammation can also drive abundant expression of growth factors and cytokines, such as transforming growth factor beta (TGF-b) and interleukin (IL)-1b, IL-4, IL-6, IL-8, IL-10, and IL-22. This expression activates several tumori-genic pathways, such as cyclooxygenase 2 (COX-2) and nuclear factor kappa B (NF-kB) subunits to promote tumori-genesis.[36] TB also causes extensive pulmonary fibrosis, which is associated with the production of TGF-b, IL-4 and IL-13.[33] Conversely, lung cancer can decrease local immunity and reactivate latent infections, or even increase the likelihood of exogenous infections.[37]

Mtb-induced chronic inflammation may be involved in the development of lung cancer through the exhausted T cell phenotype, DNA damage and repair, production of reactive oxygen species (ROS), tuberculous granulomas, formation of tuber-culous fibrosis, and infiltration of IMs. In the early stages of infection, infected MTB that undergoes endocytosis escapes the phagosomes of alveolar macrophages leading to granuloma formation, which vascularizes surrounding tissues and recruits immune cells, contributing to prolonged inflammation. Exhausted T cells enriched with granulomas and chronic ROS-induced inflammation and

release of chemical irritants promote the occurrence of lung cancer. From several studies, it shows that several expressions of immune checkpoints plays a role in inhibiting T cell responses and facilitating tumor progression (Figure 3).[23]

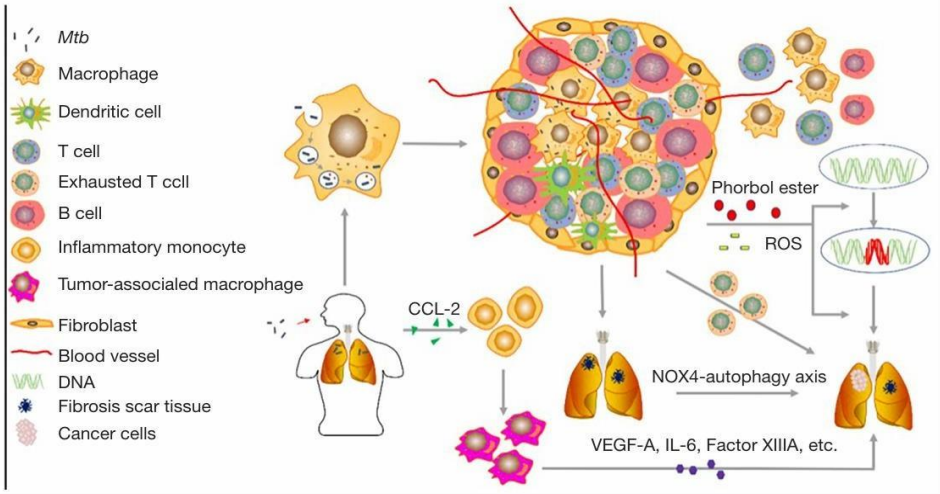

Figure 3. Chronic inflammation caused by Mycobacterium tuberculosis (MTB)[23]

b. Epidermal Growth Receptor (EGFR) Gene Mutation and Epiregulin Production. EGFR, a transmembrane glycoprotein belonging to the HER family (human EGFR-related family), participates in various biological processes, including cell proliferation and survival, and gene mutation. EGFR was the first driver mutation identified in lung cancer.[38,39] Gene amplification or mutation can result in continuously activated EGFR, leading to tumorigenesis.40 The prevalence of EGFR mutations in lung adenocarcinoma patients ranges from 10% to 78%, depending on ethnicity and geographic location, such as 30% to 40% in Asian patients and 15% in white patients.[41,42]

A study from South Korea showed that in patients with lung adenocarcinoma, pre-existing TB lesions were significantly associated with increased EGFR mutation rates, particularly exon 19 deletions.[43] In addition, patients treated with EGFR-TKIs in TB-associated adenocarcinoma had poorer treatment response and survival than patients without TB.43 Luo et al, EGFR mutation rates were significantly.[44]

Nalbandian et al. found that Mtb-infected macrophages induce DNA damage and produce a potent ligand for EGFR, epiregulin, to induce carcinogenesis.[45] Together, TB-induced EGFR mutation and epiregulin production may also contribute to carcino-genesis in the lung (Figure 4).[23]

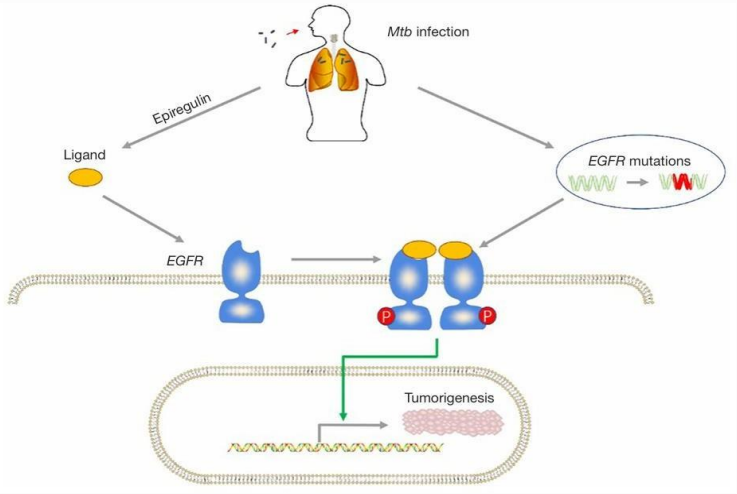

Figure 4. Epidermal growth factor receptor (EGFR) mutations induced by tuberculosis (TB) in lung cancer[23]

Tuberculosis (TB)-induced epidermal growth factor receptor (EGFR) mutations in lung cancer: EGFR autophosphorylates its tyrosine residues after binding to ligands. Activated EGFR will activate many downstream signaling pathways, such as cell proliferation, apoptosis, and survival. EGFR mutations can result in continuously activated EGFR, leading to tumorigenesis. Patients with pre- existing tuberculosis have an increased frequency of EGFR mutations, and Mtb- infected macrophages play a role in the production of epiregulin, the most potent ligand for EGFR, thus promoting lung cancer.[23]

c. Scarring/scar theory

Cancer can arise from previous pulmonary tuberculosis lesions.[46] Lung cancer can develop from fibrotic scarring caused by Mtb-induced chronic lung inflammation through mechanisms such as the NOX4 autophagy axis and this increases the tumorigenic potential of lung cells [23] Tuberculosis can cause persistent inflammation resulting in fibrosis, scarring, and destruction of host tissue. Fibrosis from old TB lesions can cause lymphadenopathy and increase carcinogen accumulation in the area. In addition, lung scarring, which results from an environment that favors spontaneous healing after recurrent pulmonary TB infection, favors tumor growth. Lung parenchyma may promote atypical epithelial cell proliferation and metaplasia in healed cavities.[46]

Simultaneous co-infection of tuberculosis and lung cancer

Patients who get comorbid tuberculosis disease with lung cancer there are several mechanisms that may occur, namely the mechanism of tumorigenesis caused by tuberculosis and the mechanism of tuberculosis induced cancer. Both can cause disease at the same time. The mechanism of tumorigenesis caused by tuberculosis can be due to the activity of T cells, myeloid derived suppressor cells (MDSC), macrophages or EGFR signals. While the mechanism of cancer-induced tuberculosis can be due to tumor effects, chemotherapy and immunotherapy.[8]

Mechanisms of tumorigenesis caused by tuberculosis[8]

a. T cells

T cells play an important role in tumor growth and metastasis. CD4+ T cells can be divided into Th1, Th2, and regulatory T cells (Treg). Th1 increase the activity of nicotinamide adenine dinucleotide NAD)-dependent silence-message regulatory factor-associated enzyme 1 (SIRT1)[47] Th2 plays an antitumor role through the expression of eosinophilic chemotactic factor (ECF), and Th2 also plays a pro-tumor role through the secretion of cytokines IL-4 and IL-5. Th1/Th2 imbalance leads to impaired immune function and promotes tumor formation.[48] TB patients exhibit a reduced Th1 response and/or increased Th2 response, and disease severity is related to Th1 response, with the lower the Th1 response, the more severe the disease.[49]

Cao et al. demonstrated that MTB can inhibit Th1 immune responses through the programmed cell death 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) protein signaling pathway, causing a Th1/Th2 imbalance and promoting lung cancer metastasis.[50] Treg can protect tumor cells by inhibiting apoptosis mediated by cytotoxic T lymphocytes (CTL).[47,48] Jie et al. showed that the percentage of Tregs in the peripheral blood of patients with active TB was significantly higher than that of the latent TB group or the control group.[51] Increased Treg activity may lead to immunosuppression and a decrease in the number of Th1 cells, which is conducive to the incidence and progression of skin cancer (Figure 5).[8]

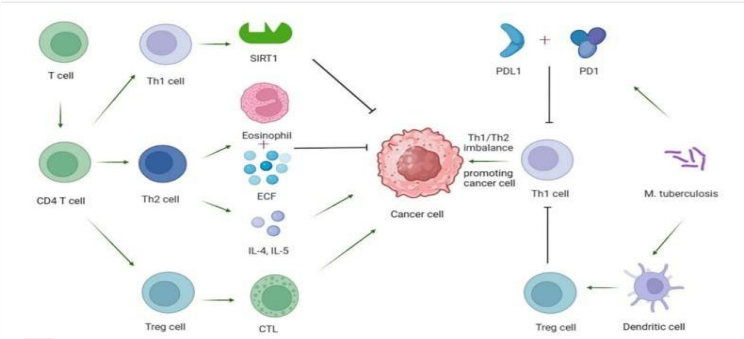

Figure 5. Mechanism of T cell influence on tumor cells and possible mechanism of MTB causing tumors.[8]

b. Myeloid derived suppressor cells (MDSC)
MDSCs are a heterogeneous group of cells from the bone marrow, which can inhibit immune cell responses through molecular reactive oxygen species (ROS) and other pathways, and have been shown to play a role in promoting malignant tumor growth and metastasis in tumor immunity.[52] This is because: in the tumor microenvironment, MDSCs inhibit excess ROS production, but MDSCs increase ROS production in a high concentration ROS environment. ROS can produce highly destructive hydroxyl radicals, resulting in damage to DNA, proteins, and lipids in the body. At the same time, jun and fos oncogenes are also activated, which even-tually leads to the occurrence of tumors.[8,53] On the other hand, maintaining an immunosup-pressor environment, MDSCs secrete a series of chemokines, thus playing a role in Treg recruitment, promoting tumor development.[48,54]

MDSCs also play an important role in chronic infectious diseases, such as TB. Studies have shown that under abnormal conditions of chronic infection such as TB, excessive production of MDSCs will lead to inhibition of host protective T lymphocyte responses.[55] The mechanism: MDSCs change the polarization direction of mono-cytes and macrophages by producing ROS, thereby inhibiting the anti-inflamma-tory response; on the other hand, studies have shown that MDSCs inhibit the immune responses of effector T cells and B cells by inducing Treg-like cells.[56] Therefore, it is very likely that MDSCs are produced after TB infection, and MDSCs ultimately promote the occurrence and progression of tumors through upregula-tion of ROS and recruitment of Treg.

c. Macrophages
Tumor-associated macrophages (TAMs) are one of the major immune cell types that infiltrate tumors and are generally divided into classically activated M1 macrophages and replacement-activated M2 macrophages. M1 functions anti- tumor, M2 promotes tumor cell formation and metastasis by inhibiting immune responses.

When the body is exposed to Mtb, macro-phages play an important role as the main innate immune cells.[8] The mechanism is likely as follows: First, it has been found that IL-37 induces macrophage polarization towards an M2-like phenotype during MTB infection.[57,58] Furthermore, it can promote the occurrence and metastasis of tumor cells.[8]

The second mechanism may be that Mtb toxic factor ESAT-6 can promote the polarization of macrophages toward pro-inflammatory M1 phenotype, and further toward anti-inflammatory M2 phenotype which also promotes the transformation of activated M1 phenotype into M2 phenotype.[59] This may play a role in promoting the development of cancer. In addition, in the inflammatory process, activated macro-phages will gather at the site of Mtb infection and produce a large amount of active nitrogen and ROS, etc. ROS promote tumor occurrence and progression by activating jun and fos oncogenes.[60]

d. Epidermal Growth Factor Receptor Signaling
EGFR signaling was shown to play an important role in regulating the prolife-ration, and differentiation of tumor cells, and is highly expressed in more than 60% of non-small cell lung cancers.[8] Mtb can cause tumors through the EGFR pathway, Nalbandian et al. found that Mtb-infected macrophages induce the production of epidermal regulatory hormone (EREG), activating the EGFR signaling pathway and promoting cancer development.45,61 Studies in mice have shown that Mtb infection stimulates EREG expression in a toll receptor 2 (TLR2)-dependent manner, and EREG binds to EGFR in a membrane or soluble form to stimulate downstream signal transduction, thereby inducing k-ras gene activation and mutation, leading to lung cancer[61] (Figure 6).

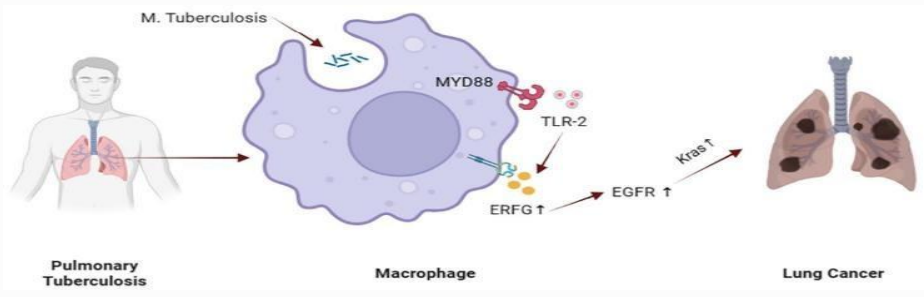

Figure 6. Possible mechanism of MTB causing tumors through the EGFR pathway[8]

A study in Taiwan evaluated the correlation of EGFR mutation outcomes in 275 TB patients, with 191 patients (69.5%) having elevated EGFR mutations in their study.[62] While it is certain that TB can induce EGFR mutations and increase the risk of tumor progression, the exact molecular mechanism remains to be further elucidated. TB not only affects EGFR mutation status, but also affects the treatment response of patients treated with EGFR tyrosine kinase inhibitors (TKIs). The concomitant use of antituberculosis drugs and TKIs in comorbid patients for EGFR-mutated lung cancer patients with active TB has shown to be a safe treatment strategy.

Mechanisms of Tumor/Cancer-Induced Tuberculosis[8]

a. Tumor effects
Currently, the mechanism of tumor-induced TB itself is not completely clear. Possible mechanisms are as follows: First, there are high levels of adenosine triphosphate (ATP) in the TME, and CD73 degrades ATP through dephosphorylation, and eventually produces adenosine.[63] Adenosine has a significant inhibitory effect on immune responses and may also play a protective role on extracellular bacteria and fungi, including MTB, by mediating type 3 immune effects.[64]

In addition, studies of lung cancer patients and mouse models have proved that lung cancer can cause a loss of microbial diversity, a reduction in the total number of bacteria, and a change in bacterial composition, which can lead to an imbalance in the microbial flora, resulting in a decrease in the stability of the body's immune homeostasis, and thus increase the host's susceptibility to various pathogens. 65 Studies have shown that up to 50%-70% of lung cancer patients develop pulmonary infectious complications during the course of the disease.[66]

b. Chemotherapy
Chemotherapy drugs have an effective killing effect on tumor cells, but affect the patient's immune system. Investigations in TB endemic areas found that TB infection is common in patients on systemic chemotherapy.[67] On the one hand, chemotherapy can produce immunosuppressive effects on cellular immunity and immunoglobulins, affecting immune function. Chemotherapy, can cause neutropenia and leukopenia leading to a severe immune deficiency state. Decreased immune deficiency makes it easier for patients to acquire infections, it also affects the normal immune defense function of the lung, thus increasing the susceptibility of the lung to bacteria including Mtb.[8] A study showed that cancer immunosuppression or anticancer chemotherapy increases the risk of TB reactivation, especially in cancer patients with previous TB.[8]

c. Immunotherapy
Immune checkpoint inhibitors (ICIs) one of the important immunotherapy therapies. ICIs mainly inhibit immune checkpoint proteins by blocking CTLA-4, PD-1, and PD-L1. ICIs affect immune function, which may increase susceptibility to Mtb infection: First, because ICIs work by blocking CTLA-4, PD-1, and PD-L1 to inhibit immune checkpoint proteins. Model studies in mice show that conditions in which CTLA-4 and PD-1 are absent can lead to homeostatic imbalanced immune system, resulting in reduced host immunity.[8,68]

Addition, pneumonia caused by ICI is the most common pulmonary toxic reaction, which may also be one of the reasons for the increased susceptibility to Mtb infection.[8] Macrophage apoptosis plays an important role in pneumonia. Through the mutual influence and stimulation of inflammation and apoptosis, macrophage apoptosis is accelerated while inflammation is aggravated.[69] After Mtb enters the body through the respiratory tract, the body mainly plays a defense role through macrophages and other cells. Therefore, macrophage apoptosis increases the risk of TB and reactivation of latent TB.[8]

Risk Factors

The following summarizes the risk factors for tuberculosis and lung cancer

Table 2. Risk factors for tuberculosis and lung cancer

Tuberculosis	Lung Cancer
1. Have lived with or frequently interacted with people who have TB. The risk of transmission depends on the length of time in close proximity, air circulation in the room, and immune levels.	1. Patients aged more than 40 years with a smoking history of 30 years or more and quit smoking within 15 years before the examination, or patients aged 20 years or more with a smoking history of 20 years. Years or older and the presence of at least one other risk factor.
2. Immunocompromized status (for example: People with HIV/AIDS, cancer, organ transplant recipients, or who take corticosteroid drugs for a long time are more susceptible to TB).	2. Exposure to radiation/atmospheric substances and work with known carcinogens (such as radon, asbestos, arsenic, bichloro methyl ether, chromium, nickel, polycyclic aromatic compounds).
3. Substance abuse: People who inject drugs or alcohol are at higher risk	3. Occupational exposure to chemical carcinogens
4. Everyone without access to adequate health services, especially children under 15 years old and young adults aged 15-44, are more vulnerable	4. History of cancer in the patient or family
5. Pre-existing medical conditions or treatment from a specialist (for example: Diabetics, chronic kidney disease, malnutrition, or those undergoing dialysis or organ transplantation are at high risk	5. Second-hand smoke environment.
6. Institutionalization: for example long- term health care facilities, mental hospitals, prisons.	6. Exposure to certain metals (chromium, cadmium, arsenic), some organic chemicals, radiation, air pollution
7. Living in densely populated neighborhoods and uninhabitable housing	7. Medical history of tuberculosis
8. Being a health worker with high-risk activities: Administration of pentamidine and other drugs, sputum induction procedures, bronchoscopy, suction, cough etiquette, managing patients with immunosuppression and administration of anesthesia and related procedures (e.g. intubation, suction)	8. Cytogenetic studies have identified many chromosomal alterations in lung cancer with numerical abnormalities and structural deviations, including deletions and translocations. Small cell lung cancer is linked to oncogenes such as c-myc, L- myc, N-myc, c-raf, and tumor suppressor genes such as p53 and Rb. Non-small cell lung cancer is linked to K-ras, N-ras, H- ras, c-myc, c-raf, and tumor suppressor such as p16 and rb genes

Source: Aribowo K, Medison I, Mizarti D, Fitrina DW. Co-Existence of tuberculosis and lung cancer. MAGNA MEDICA Berkala Ilmiah Kedokteran dan Kesehatan. 2022 Apr 9;9:51.

Several factors have been found to be associated with TB and lung cancer, including smoking, age, gender, and chronic inflammation due to Mtb infection.[9,71] According to the American Thoracic Society (ATS), the age at high risk of lung cancer is around 50 years, while TB can occur at any age.[72] Smoking is a strong risk factor for both lung cancer and TB.[9,73] Silva et al. found that, in general, patients with coexisting pulmonary TB and lung cancer were men with a history of smoking or former smoking.[74] There was a statistically significant 1.78-fold increase in lung cancer incidence in TB patients without smoking exposure, increasing to 2.93 times in smokers.[7] The increased risk of lung cancer was greatest in the first five years after diagnosis, the risk remaining 1.99 times higher for more than 20 years.[7]

Diagnostic Challenges of Lung Cancer with Tuberculosis Co-Infection

Suspicion of Lung Cancer with Tuberculosis Infection

Suspicion of patients with lung cancer and tuberculosis infection comes from radiological evidence and corresponding clinical features, especially in TB endemic areas.[75] Clinical features of pulmonary TB and lung cancer include cough, sputum, fever, hemoptysis, weight loss, and shortness of breath.[23] Due to similar symptoms, lung cancer and TB are difficult to distinguish for diagnosis. Patients with lung cancer and pulmonary TB have a higher proportion of cough but fewer night sweats than patients with pulmonary TB alone.[22,76]

The radiologic features for pulmonary TB cases are highly variable, usually in the upper lobes with cavitary lesions. In newly diagnosed active pulmonary TB, it often difficult to see concurrent lung cancer, especially in the same lobe. In a Korean study of 21 patients with pulmonary TB and lung cancer occurring in the same lobe, the diagnosis of lung cancer was delayed by an average of 11.7 months, mostly due to the occlusion of the nodules.

by TB lesions and misinterpret new lesions as worsening TB infection.[20] Compared to patients with TB alone, patients with pulmonary TB and lung cancer on CT thorax show a higher proportion of lobulated signs, masses, nodular shadows, satellite lesions, small vacuole signs, vacuole signs, spicule signs and pleural indentations, but a lower proportion of rope-like shadows and hollow lesions. [20] Whereas in TB, the main manifestations are cavitation, pleural effusion, miliary disease, lymphadenopathy and parenchymal disease.[77,78] The most frequent radiographic finding in lung cancer is a mass with or without collapse.[77] The edges of malignant tumors are uneven and form radiating threads. Hilar protrusion, pulmonary nodules, mediastinal expansion, whole or partial segmental, lobar, or pulmonary atelectasis, unresolved consolidation, cavitation, raised diaphragm, or pleural effusion are further signs of lung cancer.[77]

In newly diagnosed early-stage lung cancer, the presence of cavitary lesions, tree-in-bud appearance (peripheral "y"-shaped shadow on CT scan) and fibrocalcific foci on thoracic CT scan are indicative of possible infective agents such as TB. [79] Now that there are more sophisticated examinations with (PET)- CT for clinical staging, there are many reports that TB lesions look like lung cancer metastases.75 In particular, false-positive mediastinal lymph node metastases indicated by F-fluorodeoxyglucose (FDG) uptake are relatively common in TB endemic areas, for which a definitive diagnosis requires tissue samples by transbronchial needle aspiration guided by endobronchial ultrasonography (EBUS-TBNA).[75] This leads to a clinical diagnosis of extensive metastatic involvement of the primary lung cancer to be discovered and resected.[75]

Combined diagnosis has higher diagnostic value in lung cancer and TB, a study showed CEA, CYFRA21-1, and NSE marker examinations had high diagnostic value in lung cancer and TB patients, with a specificity of 89.9% and sensitivity of 94.9%.[80] Another study showed combined biomarkers and CT had high diagnostic value.

better. And in recent years, RNA and proteomic technologies have also been widely used in the diagnosis of TB and tumors. Some studies have applied miRNA as a new biomarker for the diagnosis and prognosis of cancer diseases, and achieved good results.[8]
In general, the presence of active pulmonary TB leads to delayed diagnosis and treatment of lung cancer. It was previously reported that active pulmonary TB in high-endemic countries worsens treatment outcomes for lung cancer patients.[81] On the other hand, the significance of coexistence of pulmonary TB and lung cancer in low-endemic countries remains unclear, as there are few reports. Contrary to previous reports, the prognosis of lung cancer was somewhat improved in the study of Lee et al, when lung cancer and active lung TB were diagnosed at the same time, patients were carefully examined and aggressively treated.[82]

The co-occurrence of TB and lung cancer may lead to an overestimation of lung cancer stage, as it is difficult to distinguish between lung cancer and TB lesions and may worsen the prognosis of lung cancer patients with active pulmonary TB.[20] Several meta-analyses have recommended that IFN-γ releasing assay (IGRA) be performed as a screening procedure prior to the initiation of systemic chemotherapy, especially immune checkpoint inhibitors (ICIs).[37] On the other hand, patients with malignant tumors are more likely to have false-negative results and weaker responses to IGRAs due to immunosuppression.[83] This is still controversial, but can be taken into consideration.

Microbiologic Confirmation of TB

Intensive sampling of sputum or other airway specimens for microbiologic examination confirms TB in patients with TB. Classical microbiologic evidence of TB in clinical or respiratory specimens consists of positive BTA microscopy, culture and identification of Mycobacterium tuberculosis (MTB) complex, and nucleic acid amplification/NAAT of Mtb. BTA positivity direct sputum or broncho-alveolar lavage, although suggestive of possible TB infection, is not found in most active TB infections, while the presence of atypical mycobacteria or non-tuberculous mycobacteria (NTM) can also lead to sputum BTA positivity. Culture is still the gold standard of microbiologic confirmation of TB infection but it takes a long time (6-8 weeks) and not all TB cases can be proven by culture.[75]

More recently, the wider use of various tests (PCR) has enabled rapid molecular testing as well as the use of GeneXpert.[75] The clinical diagnosis of TB infection can also be derived from the characteristic granulomatous inflammation (caseate) in the tissue (usually lung), when bta and/or culture results are negative. Occasionally, the first clinical suspicion of comorbid TB in early-stage lung cancer comes from pathologic evidence of granulomatous inflammation in dissected lung cancer specimens, especially in TB-endemic areas.[75]

Treatment Strategies for Lung Cancer Patients with Pulmonary TB

Current anti-TB treatment is based on WHO guidelines for TB in patients with active TB, and a combination of isoniazid, rifampicin, and pyrazinamide is used for 6-9 months.[84] If the patient is drug-resistant, the treatment regimen needs to be adjusted, and 2-5 sensitive or unused anti-TB drugs should be selected.[84] Treatment of lung cancer is more diverse, including surgery, chemotherapy and radiation therapy, targeted therapy, immunotherapy, cell therapy, and other therapies that may provide significant benefit to patients.[85]

Reports on the effectiveness and safety of therapy for pulmonary TB patients during TB treatment are limited, and there is no clear evidence. However, some reports suggest that cancer treatment does not interfere with TB treatment. In a retrospective study conducted in Japan, 30 patients with malignant tumors and TB (including 15 patients with lung cancer) reported that concurrent administration of anti-TB drugs and cytotoxic chemotherapy[86] Similarly, in a retrospective case-control study in Korea, TB that developed during chemotherapy was not clinically different from usual TB and chemotherapy did not interfere with TB treatment.[67]

Recently, it has been reported that the conversion rate of negative sputum cultures with standard TB treatment after 2 months reached 94%, even in patients with lung cancer; no significant difference was observed in the outcome of lung cancer treatment between patients with and without TB complications.[87] There are several criteria for determining when to stop or continue lung cancer treatment in patients with active TB. We need to consider the risk of transmission to medical staff, so ideally, if chemotherapy can be delayed, prioritize TB treatment. However, the priority given to TB treatment should not lead to loss of opportunity for radical treatment, such as radiation chemotherapy, therefore if radical treatment is needed immediately the patient can be hospitalized in isolation for 2 months.

A retrospective study in Japan of 24 patients with TB-associated malignancies showed that resumption of cancer treatment 2 months after completion of TB treatment may worsen prognosis and cancer progression.[87] Several papers have provided suggestions for the timing of lung cancer treatment for patients with concurrent TB. Ho et al. recommend that surgery and cytotoxic therapy be administered 2-3 weeks after starting TB treatment and that targeted therapy should be initiated while assessing drug interactions with anti-TB drugs and liver function.[75] The Japanese Society of Tuberculosis suggests that surgery be performed 4 weeks after starting TB treatment, and once confirmed BTA negative, radiotherapy can be started at the same time as TB treatment, and chemotherapy can be started 2-3 weeks after starting TB treatment.[83]

Other studies have shown that anti-TB drugs (isoniazid) can cause a decrease in white blood cells and platelets, resulting in liver damage, and cause a chemotherapy response in tumor patients, which may act as a suppressor of the therapeutic effect.[85] For patients with latent TB with lung cancer, anti-TB therapy is generally not required, but only anti-tumor therapy. For patients with active TB, both anti-tumor chemotherapy and anti-TB therapy are required.[85] For patients who require surgical resection of the tumor, preoperative tumor chemotherapy and anti-TB treatment should be synchronized, and anti-TB drugs should be continued after surgery.[8]

The following treatment flow can be used for lung cancer patients with tuberculosis infection. (Figure 7).

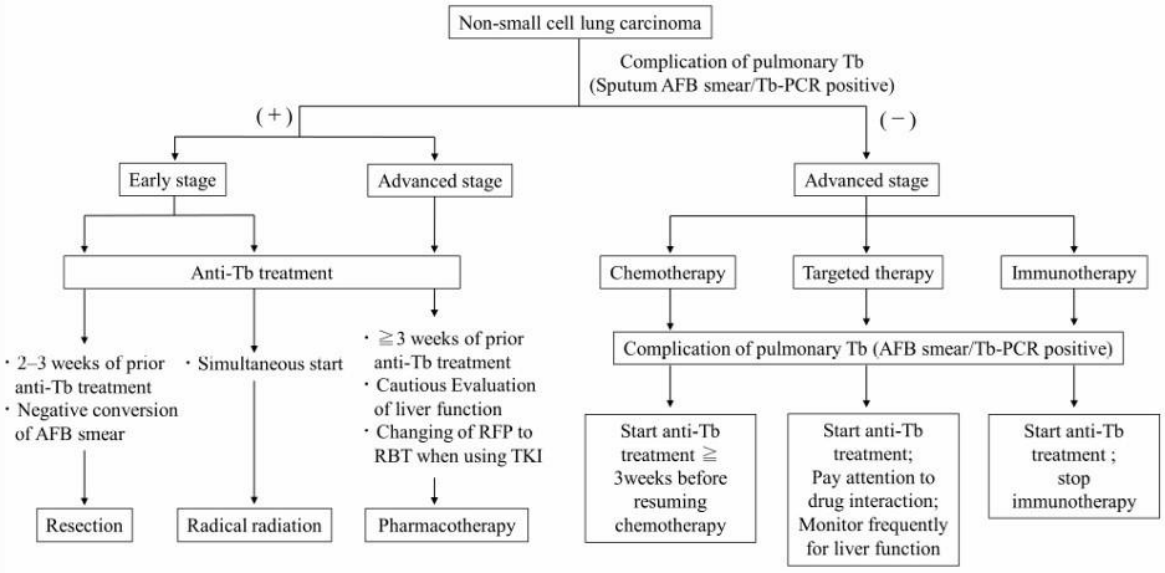

Figure 7. Suggested Algorithm for Lung Cancer Treatment Timing in Patients With Comorbid Sputum Smear/PCR Positive Active Pulmonary Tuberculosis[83]

In addition to the above algorithm there are other treatment algorithms, as follows:

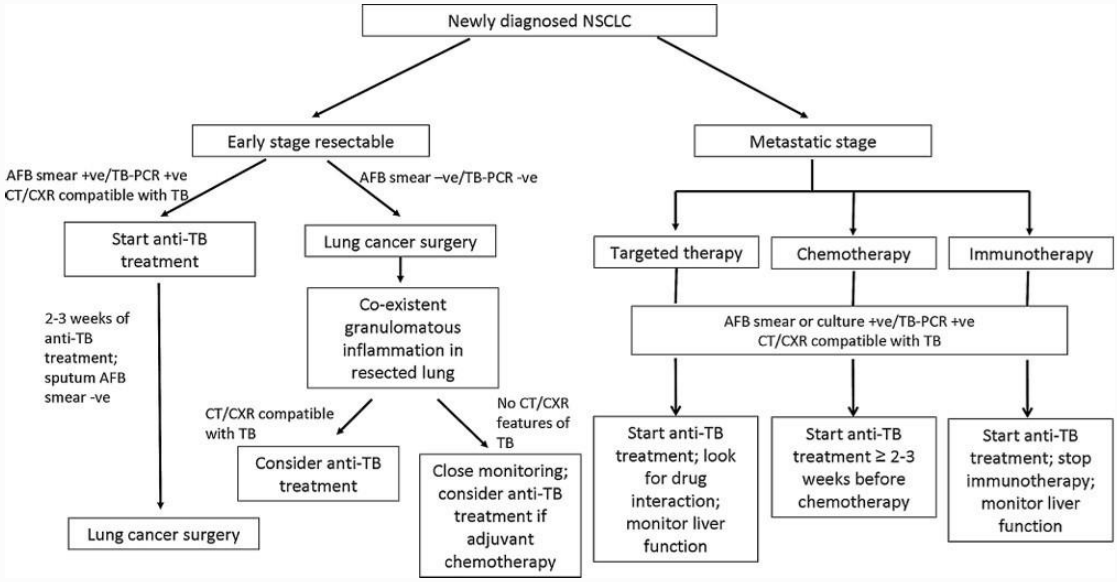

Figure 8. Suggested algorithm for diagnosis and management of tuberculosis disease and concurrent lung cancer in early stage and metastatic disease[75]

The use of immunotherapy in patients with tumors and TB should be cautious such as the use of Immune checkpoint inhibitors (ICI) or PD-1/PD-L1 treatment. Recent evidence suggests that tumor patients treated with ICIs may trigger reactivation of TB or accelerate the progression of TB infection.[88] Currently nanotechnology offers more possible strategies for the diagnosis and treatment of TCWT. Nano-dose inhalers have been developed for the treatment of lung cancer and TB, and can also be applied to patients with TB and lung cancer.[89] Clinical treatment of patients with tuberculosis comorbid lung cancer, it is necessary to consider comorbidities to develop a joint treatment strategy, and select appropriate treatment methods to play a synergistic or positive role in TB and tumors.

Interactions Between Tuberculosis Drugs and Lung Cancer

A doctor should pay attention to drug interactions when administering therapy to patients with lung cancer and tuberculosis. Among rifampicin is a strong inducer of cytochrome P450, which may reduce the effects of some anti-cancer drugs. In particular, rifampicin reduces the area under the concentration-time curve of most targeted therapies for cancer by 60-80%,[85] and caution should be exercised when using them together. Interactions between targeted therapy drugs and rifampicin are summarized in Table 3.[83]

Table 3. Drug Interactions Between Molecularly Targeted Drugs and Rifampicin

Main target	Medicine	Mediator Metabolic	Decline AUC	Decline Cmax
EGFR	Gefitinib	CYP3A4	83%	65%
	Erlotinib	CYP3A4	69%	39%
	Ceritinib	P-glycoprotein	34%	22%
	Dacomitinib	CYP2D6	no data	no data
	Osimertinib	CYP3A	78%	73%
ALK	Alectinib	CYP3A4	73%	51%
	Lorlatinib	CYP3A, UGT1A4	85%	76%
	Brigatinib	CYP2C8, CYP3A4	80%	60%
	Ceritinib	CYP2C9, CYP3A4	70%	44%
ROS-1	Crizotinib	CYP3A4	84%	79%
ROS- 1/NTRK	Entrectinib	CYP3A	77%	55%
BRAF	Dabrafenib	CYP2C8/9, CYP3A4	34%	27%
	Trametinib	CYP2B6, CYP3A4	no data	no data
MET	Tepotinib	CYP2C8/9, CYP3A4	no data	no data
	Capmatinib	CYP3A4	67%	56%
RET	Selpercatinib	CYP3A4	87%	70%
KRAS	Sotorasib	CYP3A	51%	35%
HER2	Trasruzumab	CYP3A	no data	no data

Note: AUC*: area under the concentration-time curve. Cmax maximum plasma concentration,* EFGR*: epidermal growth factor receptor,* ALK*: anaplastic lymphoma kinase,* ROS-1, *c-ros oncogene 1;* NTRK*, neutrophic receptor tyrosine kinase,* BRAF*, B-raf proto-oncogene, serine/threonine kinase;* MET*: mesenchymal-epithelial transition,* RET*: rearranged during transfection,* KRAS*: v- Ki-ras2 Kirsten rat sarcoma viral oncogene homolog;* HER2*: human epidhermal growth factor type 2;* CYP*: cytochrome P450;* UGT, *UDP-glucoronosyl transferase*.

Source: Otoshi R, Ikeda S, Kaneko T, Sagawa S, Yamada C, Kumagai K, et al. Treatment Strategies for Non-Small-Cell Lung Cancer with Comorbid Respiratory Disease; Interstitial Pneumonia, Chronic Obstructive Pulmonary Disease, and Tuberculosis. Vol. 16, Cancers. Multidisciplinary Digital Publishing Institute (MDPI); 2024

Conclusions

1. Tuberculosis and lung cancer are two diseases with high incidence and mortality rates, with similar clinical symptoms and radiological features.
2. Tuberculosis and lung cancer interact and influence each other, suggesting that TB and cancer should be diagnosed and treated holistically.
3. Integrated and individualized treatment protocols should be developed for patients with the aim of effectively enhancing therapeutic effects and improving prognosis.

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