Review Article

Immunomodulatory effects of intestinal lung axis microecology and other factors on the prognosis of advanced non-small cell lung cancer

Changxing Shen, Yanbei Ren, Xu Zhang, Qing Xia, Ming Li, Changhui Wang, Lihong Fan

Department of Respiratory and Critical Care Medicine, The Tenth People's Hospital affiliated to Tongji University, Shanghai 200072, China

Contributions: (I) Conception and design: L Fan; (II) Administrative support: C Wang; (III) Provision of study materials or patients: X Zhang; (IV) Collection and assembly of data: Y Ren; (V) Data analysis and interpretation: Q Xia; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Lihong Fan. The Tenth People's Hospital affiliated to Tongji University, Shanghai 200072, China. Email: fanlih@aliyun.com.

Abstract: Overall survival (OS) of lung cancer varies greatly with individual patients in the global setting. Multiple factors may affect the prognosis. Different antibiotics have significant effects on the prognosis of lung cancer patients. The intestinal microbiome, nutritional status and inflammatory factors all have significant impact on OS of lung cancer patients.

Keywords: Non-small cell lung cancer (NSCLC); antibiotics; intestinal microecology; inflammatory immunity

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Introduction

A study published on *CA*: *A Cancer Journal for Clinicians* in 2016 reports that lung cancer ranks first among the top five cancer deaths in China (1). Non-small cell lung cancer (NSCLC) is the most common histological type of lung cancer, accounting for approximately 80% of all lung cancers, and about 70% of patients diagnosed with advanced disease (2). The overall survival (OS) of patients with advanced NSCLC is relatively short. The median survival time of terminal NSCLC has extended to about one year, but in our clinical practice we sometimes met with patients with advanced NSCLC who had survived longer periods. According to the statistics, 10–21% patients with advanced lung cancer had a survival period of more than two years (3). In this review, we intend to discuss differences in prognosis and OS between patients with advanced NSCLC, and factors affecting OS to see whether the development and progression of lung cancer had any significant correlation with the use of antibiotics, intestinal microecology, albumin and fibrinogen levels, and inflammatory immunity, knowing that inflammatory immunity imposes a great impact on pulmonary adenocarcinoma patients (4), and dissecting that microecology of the intestinal lung axis affects the development of NSCLC through immunoregulatory mechanisms (5,6).

Immunomodulatory effects of intestinal lung axis microecology on NSCLC

The function of microorganisms related to the gastrointestinal tract includes disruption of the reduction in complex dietary polysaccharides to compete with pathogens, and regulation of the intestinal mucosa and immune system. A large body of evidence suggests that host epithelial cells and other immune cells can regulate inflammatory responses directly from microbes and accompanying local cytokines. This form of immune response often occurs in organs such as the lungs (7-10). In April 2017, Lyon published an article reporting that microbes in the lungs are not the only cause of pneumonia, and microbes in the gut seem to have an effect on lung health (11), suggesting that there is a close relationship between intestinal microecology and lung microecology, and that alterations in intestinal flora can cause changes in lung immunity and microecology (12).

Vétizou *et al.* found that oral probiotics could promote $CD8^+$ T cell accumulation in the tumor area and enhance the anti-tumor effect of PD-L1 monoclonal antibody in a melanoma mouse model (13). Another animal experiment (14) demonstrated that treatment of tumors with CLA-4 was dependent on the intestinal flora because it did not produce an effective anti-tumor effect in the absence of the intestinal flora. The results of a series of animal studies showed that the symbiotic microbiota contributed to the immune enhancement against lung cancer. Probiotics adjuvant chemotherapy could enhance the anti-tumor and pro-apoptotic effect of carboplatin, and this immune enhancement and anti-tumor effect mainly relies on acidophilia. Lactobacillus up-regulated the expression of IFN-γ (interferon), GZMB (granzyme B) and PRF1 (perforin) by $CD8^+$ T lymphocytes, and down-regulated VEGFR (vascular endothelial growth factor receptor) expression in tumor-bearing mice (15). Cheng *et al.* (6) demonstrated that the expression of γδ T lymphocyte immunodeficiency interleukin-6 (IL-6) and IL-23 was decreased in antibiotic-treated mice, and the immune surveillance was reconstituted after IL-17 supplementation. Excessive antibiotic treatment can destroy the symbiotic microbial flora on the mucosal surface, thus increasing the susceptibility of the occurrence of tumors. In short, intestinal microbes and lung diseases interact, and intestinal probiotic regulation can enhance the anti-tumor immunity of lung cancer and enhance the anti-tumor effect of chemotherapy drugs. Imbalance of the body micro-ecology increases the risk of lung cancer.

Prognostic mechanisms of antibiotic therapy for advanced NSCLC

Advantages and disadvantages of antibiotics for treatment of pulmonary infection in patients with NSCLC

Pulmonary infection is one of the most common complications in patients with advanced NSCLC. Severe lung infections impose a detrimental effect on OS of patients with advanced NSCLC. Antibiotic treatment can control lung infection and prolong OS of such patients. Obstructive pneumonia is a common complication of patients with NSCLC. A small number of data from bacteriological studies of obstructive pneumonia suggest that most of these infections are essentially caused by multiple microorganisms. Two small studies (16) compared the microbial population obtained by ultrasound-guided needle aspiration tissue culture with that obtained from sputum culture and found that 30–55% of the needle culture results were composed of various microorganisms that were incomparable to the flora isolated from the sputum culture. A large retrospective study by Kohno *et al.* (17) also found that most lung cancer patients were infected with various microorganisms, and the most common florae were *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Acinetobacter*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. The results of the existing clinical studies (18) showed that Gram-negative bacilli infection is the most common type of infection in nosocomial infections in patients with NSCLC. Most of our information on empirical antibacterial therapy for obstructive pneumonia is inferred from high-stake populations with chronic airway inflammation, and bronchoscopy for obstructive pneumonia plays an important role in the management of obstructed airways. In particular, it has an important value in obtaining pathogenic therapy (19). In the past two decades, chances of Gram-positive bacilli infection have increased and the proportion of Gram-negative bacteria has also decreased, mainly due to our sensible choice of empirical anti-infective treatment options for obstructive pneumonia. Pulmonary infection is one of the common complications of chemotherapy, and may lead to death in severe cases. The major aim of infection prevention programs is to enhance autoimmunity and optimize the efficacy of antibiotic therapies, usually by selecting broad-spectrum antibiotics. Both protocols have been shown to reduce the incidence of infection (20,21). The prolongation of OS in patients with advanced NSCLC is partly due to the effective treatment of pulmonary infection. However, two studies from Chinese researchers (22,23) showed that excessive antibiotic use in patients with terminal NSCLC increased the risk of recurrence of lung infection, especially when combined antibiotics were used for a long time. For this reason, the use of antibiotics in patients with advanced NSCLC should be controlled strictly. It is recommended that antibiotics should be used only in patients with unequivocal or severe infections, and it is recommended that combination use of broad-spectrum antibiotics should be avoided whenever possible (24).

Repeated antibiotic exposure may increase cancer risk and reduce immune response in patients with advanced NSCLC

As antibiotics do not have known direct carcinogenic effects, our main hypothesis is focused on the effects of antibiotics on the composition of human microbiota. Antibiotic abuse

or antibiotic overuse is known to induce bacterial diversity persistently (25-27). Flora disorders can induce chronic inflammation (28) and affect the body's metabolism by activating genes involved in insulin resistance and cell proliferation, thus affecting the immune system against cancer. Some bacteria may even have a direct carcinogenic effect on epithelial cells. Microbiota may also participate in carcinogenesis in individuals with specific genetic or immune predisposition. The carcinogenic mechanism of antibiotics still needs further rigorous design. Boursi *et al.* (29) analyzed 125,441 cases and 490,510 matched controls and found that penicillin, cephalosporin or macrolides increased lung cancer risk, and there was a correlation between antibiotic regimens and cancer risk, especially for gastrointestinal and lung tumors. Importantly, there is no evidence to support an association between the use of antiviral and antifungal drugs and the increased risk of cancer.

Non-tuberculous mycobacterial (NTM) lung infection is associated with the development of lung squamous cell carcinoma

Lande *et al.* (30) retrospectively studied the sputum culture of 845 sufferers with newly diagnosed pulmonary squamous cell tumor and found that the presence of *Mycobacterium avium* complex (MAC) in sputum cultures was particularly associated with the disease. These observations could not help postulate that this association may explain why lung squamous cell carcinoma and peripheral lung squamous cell carcinoma often occur in patients who do not smoke, especially in elderly patients. But as MAC usually affects the distal airway, this possible association between MAC infection and lung cancer deserves further investigation because there is a lack of statistical evidence to support the association and/or causality between MAC lung infection and lung cancer.

Aerosolized antibiotics or probiotics enhance lung tumor immune activity

Le Noci *et al.* (31) demonstrated that antibiotics regulated lung microbiota in a mouse animal experiment. They found that probiotic aerosolization reduced lung tumor growth, and that antibiotic treatment decreased lung immunosuppressive cells, and probiotics promoted the maturation of resident antigen presenting cells. In the lungs of vancomycin/neomycin aerosolized mice, bacterial load and regulatory T cell reduction were associated with enhanced activation of T cells and NK cells. A reduction in melanoma lung metastasis also occurred in the lungs where antibiotics were administered to treat bacterial isolates. The aerosolized *Lactobacillus rhamnosus* also strongly promoted immunity to melanoma lung metastasis. It is noteworthy that animal experiments have shown that ceftriaxone has an anti-tumor effect, the main mechanism of which is believed to be through direct binding of ceftriaxone to Aurora B to inhibit its activity *in vitro* and in cells. Aurora B was found to be expressed abundantly in pulmonary carcinoma cell clones, which may be related to the occurrence and development of tumors (32).

The use of antibiotics does not affect the efficacy of the PD-1 inhibitor nivolumab in patients with NSCLC

Kaderbhai *et al.* (33) observed that antibiotics did not impact the progression-free survival (PFS) under nivolumab, and that antibiotic-induced microbial changes did not appear to interpose the work of nivolumab in NSCLC patients. But as the sample size of their study is small, larger-scale controlled clinical studies are required to confirm whether antibiotics have an effect on the efficacy of PD-1 inhibitors.

The value of biomarkers in predicting survival of advanced NSCLC patients

NSCLC accounts for approximately 85% of primary lung cancers (33). Despite advances in early detection and multiple treatments, the prognosis of patients with NSCLC remains poor, with a 5-year OS of 18.2% (34). Therefore, it is important to identify promising prognostic biomarkers to help tailor the treatment that is most beneficial to NSCLC patients. Zhang *et al.* (35) identified CAR [C-reactive protein (CRP) to albumin ratio] and NLR (neutrophil to lymphocyte ratio) as independent prognostic factors for disease-free survival (DFS) and OS in patients with operable NSCLC. With pathological factors and other factors adjusted, elevated CAR and NLR were found to be associated with poor tumor prognosis. Another study in patients with palliative care for late stage NSCLC (36) also suggested that the CRP/Alb ratio was significantly associated with poor prognosis. The correlation between elevated NLR level and poor tumor prognosis may be explained by an increase in neutrophils or lymphopenia that may produce cytokines, inhibition of lymphokine-activated killer cells, and promotion of cancer progression. CAR elevation may explain why the inflammatory state of the body can actively promote the development of cancer. A

low level of albumin suggests strong proliferation of tumor cells or low resistance of the body to tumor growth due to malnutrition. OS of such patients is usually not long. Alifano *et al.* (37) studied the clinical, pathological and laboratory data of 300 patients who underwent surgery for NSCLC and found that CRP level was significantly associated with chronic bronchitis, hypoproteinemia, pathological stage and vascular embolization around the tumor. The 5-year survival rate of patients with preoperative CRP ≤3, 4–20 and >20 mg/L was 55.6%, 45.6% and 40.0% respectively. A CRP level greater than 20 mg/L also indicated a worse survival rate. Overall, CRP and lymphocytes reflect the chronic inflammation level of the body, and higher levels of inflammation suggest a poor prognosis. Thrombocytopenia and coagulation system activation are usually affected by chronic inflammation, which is associated with disease progression and considered to be a poor prognostic factor in patients with malignant tumors. Another study (38) reviewed the initial platelet count and fibrinogen level in 854 histologically confirmed NSCLC patients and found that platelet count >450×10^9/L and serum fibrinogen level >4.5 g/L were associated with poor prognosis. In addition, positive D-dimer before and during chemotherapy is a predictor of therapeutic response and PFS deterioration in patients with advanced NSCLC (39). Thrombocytopenia and activation of the coagulation system are not dependent on tumor burden or clinical stage, but may represent individual tumor characteristics. The pathophysiological mechanisms of thrombocytosis and high fibrinogen level in cancer patients are associated with tumor-driven humoral factors such as IL-6, IL-1 and macrophage colony-stimulating factor. Studies have shown that tumor cells release IL-6, which stimulates megakaryocyte production. The adhesion of platelets to tumor cells in peripheral blood can prolong the survival of tumor cells and enable them to adhere to the vessel wall. In addition, platelet-derived endothelial cell growth factor induces angiogenesis *in vitro* and *in vivo*. The mathematical methods can be used to calculate the prognosis of NSCLC by calculating the CRP, NLR, platelet count, fibrinogen value and D-dimer value. The above biomarkers are easy to obtain in clinical practice, and the operating procedures are simple and practical.

Albumin-bound paclitaxel has a favorable effect on advanced NSCLC and improves the quality of life

A clinical observational study of 537 patients (40) showed that albumin-bound paclitaxel as a first-line treatment for elderly patients with advanced NSCLC could increase the objective response rate, OS and the quality of life of the patients. The advantage may be attributed to the altered distribution of pharmacokinetic drugs by albumin-bound paclitaxel, which may help reduce the incidence of neuropathy, reduce the amount of medication, attenuate the toxic adverse effects, and improve patient tolerance.

Advanced NSCLC patients with metabolic disease have a worse prognosis

Some studies (41) have also shown that obese cancer patients have lower survival rates. Obese patients face several specific challenges associated with cancer diagnosis and treatment. Chemotherapy and hormonal therapy in obese patients are affected by changes in pharmacokinetics and hormone levels. In addition, the accuracy of radiation therapy may be adversely affected in this population due to greater skin movement and increased movement of internal organs. In addition, obese patients, especially those with pathological obesity, are usually complicated with sleep apnea hypopnea syndrome or chronic obstructive pulmonary disease. The chronically inflammatory body is susceptible to the development of cancer and not conducive to prognosis. When encountering such patients, clinicians need to improve the hypoxic state and reduce the state of oxidative stress of the body (42-44).

Conclusions

The effects of repeated exposures to antibiotics and intestinal micro-ecological adjustment on the prognosis of advanced NSCLC await confirmation from more clinical studies. There are insufficient experimental data on the use of probiotics for the treatment of lung cancer. Future clinical and basic research in this field should be strengthened to further investigate the effects of repeated exposure to antibiotics on the prognosis of advanced NSCLC and explore the therapeutic value of probiotics for advanced NSCLC.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.09.32). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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