



Distribution of pathogenic bacteria in lower respiratory tract infection in lung cancer patients after chemotherapy and analysis of integron resistance genes in respiratory tract isolates of uninfected patients

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Background: We studied the distribution of pathogenic bacteria in lower respiratory tract infection in lung cancer patients after chemotherapy and analyzed the integron resistance genes in respiratory tract isolates of uninfected patients.

Methods: Retrospective analysis was used to select sputum samples from 400 lung cancer patients after chemotherapy admitted in Fuyang People's Hospital from July 2017 to July 2019. Culture, isolation and identification of strains were conducted in accordance with the national clinical examination operating procedures.

Results: A total of 134 strains were identified. In 120 patients with pulmonary infection, 114 strains were cultured. Twenty strains of *Klebsiella pneumoniae* were cultured in 280 patients without pulmonary infection. Among the 134 strains, the detection rate of gram-negative bacteria was 79.10%. The first four strains were *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*. The gram-positive bacteria detection rate was 4.47%, mainly *Staphylococcus aureus* and *Streptococcus*. The fungus detection rate was 16.42%. The drug sensitivity results showed that the resistance rate of gram-negative bacillus to penicillin and cephalosporin was higher, and were more sensitive to carbapenem, piperacillin tazobactam and cefoperazone sulbactam. Gram-positive cocci were resistant to penicillin, macrolide and clindamycin, and sensitive to linezolid, vancomycin and rifampicin. All strains of fungal culture were *Candida albicans*, which were sensitive to common antifungal drugs. Among the 20 strains of *Klebsiella pneumoniae* cultured in sputum specimens of non-infected patients with lung cancer undergoing chemotherapy, 2 strains were integron-positive strains, and all of them were class I integrons.

Conclusions: Lung cancer patients after chemotherapy have a high resistance to commonly used antimicrobial drugs, so it is necessary to detect the resistance of pathogenic microorganisms in clinical practice. The strains carried by patients with lung cancer without pulmonary infection during chemotherapy can isolate type I integrons, suggesting that the spread of drug resistance at gene level should be closely detected.

Keywords: Lung cancer; chemotherapy; pulmonary infection; integron; resistance gene

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Introduction

In recent years, the incidence and mortality of lung cancer have become the highest among malignant tumors (1-3). Early stage lung cancer patients always have no symptoms, so most lung cancer patients are in the middle or late stage when detected and lost the opportunity of surgical treatment, chemotherapy is the classic treatment for these patients. In recent years, immunotherapy is rising gradually and becomes a new choice (4-6). The immunity of patients with lung cancer, especially in patients after chemotherapy, is very low, so the patients of lung cancer treated with chemotherapy are more easily to suffer pulmonary infection (7). Meanwhile, pulmonary infection is one of the causes of death in patients with lung cancer undergoing chemotherapy (8). Therefore, it is necessary to monitor the drug sensitivity of pathogens in patients with lung cancer complicated with pulmonary infection after chemotherapy. Previous studies on drug resistance of bacteria mainly focused on gene mutation of bacterial chromosome, but this kind of bacterial drug resistance caused by gene mutation cannot be transmitted. Studies have found that the reason for most bacteria to develop drug resistance is to obtain exogenous drug resistance genes (9). It has been shown that drug resistance genes can be transmitted horizontally through conjugated plasmids, transposons and integrated phages (10-12). Stokes and colleagues first reported integron, which was related to the horizontal transmission of drug resistant genes (13-15). Integron is a kind of movable gene element, carrying site-specific recombination system components, which can integrate many drug-resistant gene cassettes together to form multiple drug resistance. It plays an important role in the spread of drug-resistance of bacteria, especially gram-negative bacteria (16). A lot of studies have researched the isolated strains of infected patients; few of them pay attention to the integron carried by the respiratory tract strains of uninfected patients. Many kinds of hospital strains can be planted in the respiratory tract of patients undergoing chemotherapy, who have been hospitalized for several times. In order to better monitor and control the spread of bacterial resistance, the integron carried by the isolated bacteria of respiratory tract samples of lung cancer patients without pulmonary infection after chemotherapy is detected. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-928>).

Methods

Patient collection

We collected 400 patients who were hospitalized in Fuyang People's Hospital from July 2017 to July 2019. All patients were diagnosed with lung cancer and received chemotherapy. Pulmonary infection was diagnosed according to the relevant diagnostic criteria of respiratory branch of Chinese Medical Association. The patients present COPD are excluded. Among the patients, 261 were male and 139 were female. The average age was (56±9.5) years. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients provided written consent. The study was approved by the Ethics Committee of Fuyang People's Hospital.

Sputum collection

Patients were rinsed with normal saline in the morning, and the deep cough sputum was kept in a sterile sputum box for examination within 1 hour. The strain was identified by the bacterial identification system of Biomerieux of France. The K-B method recommended by WHO was used to detect the sensitivity of the strains to antibiotics. The quality control strains were *Klebsiella pneumoniae* ATCC700603, *Escherichia coli* ATCC25922, *Staphylococcus aureus* ATCC25923, *Streptococcus pneumoniae* ATCC29213, *Pseudomonas aeruginosa* ATCC27853 and *Candida albicans* ATCC10231. The standard reference strain and the experimental strain were determined in parallel during the experiment.

Preparation of total bacterial DNA

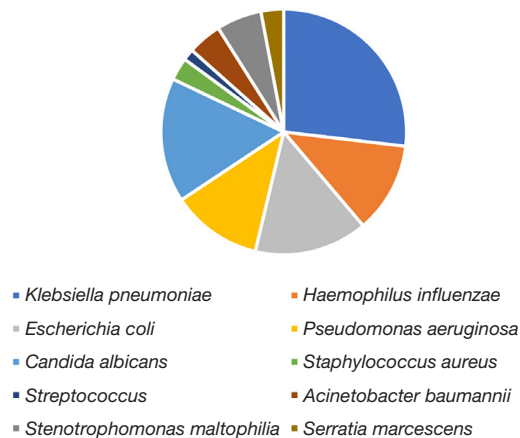
The bacterial DNA was extracted according to the operating instructions of the bacterial DNA extraction kit and analyzed by electrophoresis.

Integron detection and classification

To detect integron, the class I, class II and class III integrase genes in the 5' conserved region of integron were amplified simultaneously by annexation primers, this process also known as integrase gene polymerase chain reaction (PCR) (17). The sequence of the upstream primer hep35 was 5'-tgccgggyarargatbtkgatt-3', and the sequence of the downstream primer hep36 was 5'-carcatgcgtrtaat-3'. The expected amplification fragment is 491 bp, the amplification system contained 25 µL premix Taq, 2 µL template,

Table 1 Detection rate of population pathogen (%)

| Pathogenic bacteria | Strains | Detection rate |
|------------------------|---------|----------------|
| Gram-negative bacteria | 106 | 79.10 |
| Gram-positive bacteria | 6 | 4.47 |
| Fungus | 22 | 16.42 |

**Figure 1** The number of pathogenic bacteria was detected.

1 μ L upstream and downstream primers each, 21 μ L sterile distilled water, the total circulation system was 50 μ L. The amplified products of integrase PCR were analyzed by restriction endonuclease Hinf I digestion. 2 μ L 10 \times H Buffer, 1 μ L Hinf I enzyme and 8 μ L PCR product were bathed in water at 37 degrees centigrade for 4 hours together. The enzyme products were analyzed by agarose 2% gel electrophoresis. According to the results of electrophoretic, class I integron was defined as a 491 bp fragment of the amplified product of integrase PCR after digestion.

Statistical analysis

SPSS 17.0 was used to perform statistical analysis. We analyzed the detection rate of population pathogen and drug resistance rate of different bacteria.

Results

Patient clinical data

We collected 400 patients who were hospitalized in Fuyang People's Hospital from July 2017 to July 2019. Among the

patients, 261 were male and 139 were female. The average age was (56 \pm 9.5) years. Twenty-five of the patients had high blood pressure and the blood pressure was well controlled. None of them had mellitus diabetes or some other co-morbidities.

Distribution of pathogenic bacteria in respiratory tract of patients with lung cancer after chemotherapy

One hundred and thirty-four strains were identified in 400 patients after chemotherapy. There were 120 patients with pulmonary infection, 114 strains were cultured. Among 280 patients without pulmonary infection, 20 strains were cultured; all of them were *Klebsiella pneumoniae*. Among the 134 cultured strains, the detection rate of gram-negative bacteria was 79.10%, and the top four were *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*. The detection rate of gram-positive bacteria was 4.47%, mainly were *Staphylococcus aureus* and *Streptococcus*. Twenty-two strains of fungi were detected, all of them were *Candida albicans*, and the detection rate was 16.42% (Table 1, Figure 1).

Drug resistance rate of gram-negative bacilli

As shown in Table 2, gram negative bacteria (106 strains) had high resistance to penicillin and cephalosporins, and high sensitivity to carbapenems, piperacillin tazobactam and cefoperazone sulbactam.

Drug resistance rate of gram-positive bacteria

Gram positive bacteria (6 strains) had high resistance to penicillin, macrocyclic lipids and clindamycin, and were sensitive to linezolid, vancomycin and rifampicin (Table 3).

Drug resistance rate of fungi

Table 4 showed that all fungi (22 strains) were *Candida albicans*, which were sensitive to common antifungal drugs.

Integron detection and classification

Twenty strains were cultured in 280 patients without pulmonary infection, which were all *Klebsiella pneumoniae*, among them, 2 strains were integron positive, all of which were class I integron.

Table 2 Drug resistance rate of major gram-negative bacteria (%)

| Antibacterial agents | <i>Klebsiella pneumoniae</i> | <i>Escherichia coli</i> | <i>Pseudomonas aeruginosa</i> | <i>Haemophilus influenzae</i> |
|---------------------------------------|------------------------------|-------------------------|-------------------------------|-------------------------------|
| Ceftazidime | 58.9 | 56.1 | 45.2 | 34.6 |
| Ceftriaxone | 69.2 | 70.2 | 55.1 | 54.2 |
| Cefuroxime | 60.1 | 58.1 | 65.2 | 64.3 |
| Cefepime | 45.8 | 32.3 | 31.5 | 30.1 |
| Cefoxitin | 48.4 | 45.6 | 65.2 | 45.2 |
| Amikacin | 33.3 | 36.8 | 34.2 | 23.1 |
| Levofloxacin | 45.5 | 56.8 | 65.2 | 23.8 |
| Smzco | 13.5 | 10.5 | 34.1 | 45.6 |
| Tigecycline | 0 | 0 | 0 | 0 |
| Amoxicillin and clavulanate potassium | 89.4 | 100 | 90.2 | 30.2 |
| Cefoperazone and sulbactam | 10.2 | 34.3 | 11.3 | 9.3 |
| Tazobactam and piperacillin | 23.5 | 30.2 | 23.3 | 10.1 |
| Ertapenem | 0 | 0 | 0 | 0 |
| Imipenem | 0 | 0 | 0 | 0 |
| Cefuroxime axetil | 60.5 | 63.2 | 45.6 | 34.5 |

Table 3 The main resistance rate of gram-positive bacteria (%)

| Antibacterial agents | <i>Staphylococcus aureus</i> | <i>Streptococcus</i> |
|----------------------|------------------------------|----------------------|
| Oxacillin | 100 | 100 |
| penicillin | 100 | 100 |
| Gentamicin | 23.5 | 34.8 |
| Rifampicin | 12.5 | 20.9 |
| Ciprofloxacin | 80 | 78.5 |
| Levofloxacin | 86.6 | 60.5 |
| Moxifloxacin | 34.8 | 23.8 |
| SMZco | 23.5 | 45.5 |
| Clindamycin | 100 | 100 |
| Erythromycin | 100 | 100 |
| Linezolid | 0 | 0 |
| Vancomycin | 0 | 0 |
| Tetracycline | 100 | 100 |
| Tigecycline | 0 | 0 |

Table 4 Drug resistance rate of fungus

| Antibacterial agents | <i>Candida albicans</i> |
|----------------------|-------------------------|
| Amphotericin B | 0 |
| 5-fluorouracil | 0 |
| Voriconazole | 0 |
| Fluconazole | 4.5 |
| Itraconazole | 0 |

Discussion

Chemotherapy is one of the most important treatment methods of advanced lung cancer patients (4-6). However, after chemotherapy, the white cell count of some patients will decrease, the hospitalization time will be extended, and not only the cancer cells but also the normal immune cells will be killed at the same time, thus the lung cancer patients are prone to suffer pulmonary infection after chemotherapy (18). In turn, it is necessary to research the

pathogen distribution and drug resistance of pulmonary infection in patients with lung cancer after chemotherapy, which is helpful to guide the clinical rational use of various antibacterial drugs to effectively control infection and eventually reduce the mortality of patients.

In this study, 134 strains of pathogenic bacteria were isolated from the respiratory secretion of 400 patients with lung cancer after chemotherapy. Among them, 106 strains were gram-negative bacteria (79.10%), 22 strains were fungi (16.42%) and 6 strains were gram-positive cocci (4.47%). The results displayed that the pathogens of lung cancer patients with pulmonary infection after chemotherapy were quite different from those of community acquired pneumonia. Studies have shown that the most common pathogens of community acquired pneumonia are *Streptococcus pneumoniae*, *Haemophilus influenzae* and atypical pathogens (19-21). It's better to choose the antibiotics for gram-negative bacilli before the drug sensitivity results come out for lung cancer patients with pulmonary infection after chemotherapy. Compared with other related reports, the detection rate of fungi is higher, while that of gram-positive cocci is lower. The following factors may be related to as followed; first of all, chemotherapy can decrease the number of leukocyte and granulocyte, which will reduce the immunity of patients, so the patients have high risk to get fungal infection. Besides, in the long-term and repeated infection of lung cancer patients, broad-spectrum antibiotics will be used in clinical, which results in the long-term use of antibiotics and increases the possibility of fungal infection. Fungal infection is one of the causes of death in patients with low immunity. It has been found that fungi could produce drug resistance through many mechanisms. There are few drugs to choose in clinical in the treatment of fungal infection, and the fungi are prone to get cross resistance to antifungal drugs, which makes the treatment more difficult in lung cancer patients after chemotherapy (22,23).

In the research, we found that among the 106 strains, the main gram-negative bacteria were *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Haemophilus influenzae*. They were highly resistant to penicillin and cephalosporins, and sensitive to carbapenems, piperacillin tazobactam and cefoperazone sulbactam, suggesting that the above three drugs can be used as the first choice for the treatment of pulmonary infection of lung cancer patients after chemotherapy. The result showed that the gram-positive bacteria were *Staphylococcus aureus* and *Streptococcus pneumoniae*, and the detection rate of them was relatively low. This result was considered to be related to the

distribution of local pathogenic bacteria and the selection and application of antibiotics.

From *Table 2*, we could see that the strains were highly resistant to penicillin and cephalosporin, and no strains resistant to linezolid and vancomycin were found. Thus, this kind of antibiotics is the first choice to treat multi-resistant *Staphylococcus aureus* and *Streptococcus*. We found that the detection rate of fungi was very high, which might be related to the low immunity of lung cancer patients after chemotherapy. It could be seen from *Table 3* that, the fungi were sensitive to common antifungal drugs, such as fluconazole, voriconazole and itraconazole, so the common antifungal drugs could be selected to treat fungal infection in clinical.

In recent years, the detection rate of carbapenem resistant *Enterobacteriaceae* (CRE) is increasing. The treatment of infection caused by CRE is limited, leading to the high mortality (24,25). We found that 20 strains were isolated from respiratory tract of patients without pulmonary infection, and all of them were *Klebsiella pneumoniae*. *Klebsiella pneumoniae*, belonging to *Enterobacteriaceae*, is the most important conditional pathogen in iatrogenic infection except *Escherichia coli*. Severe or elderly patients are more susceptible to *Klebsiella pneumoniae* (26). With the wide use of antibiotics, *Klebsiella pneumoniae* resistant strains continue to increase. The monitoring and the mechanisms of drug resistance of *Klebsiella pneumoniae* has become the focus of international medicine (27-29).

Some studies have shown that the drug resistance of clinical pathogens, environmental bacteria, animals and normal human flora is increasing with the extensive and excessive use of antibiotics (30). Integron plays a pivotal role in the acquisition and transmission of drug resistance genes. The resistance rate of integron positive strains is significantly higher than that of integron negative strains (13). Therefore, the detection of integron in uninfected patients is conducive to monitoring the spread of drug-resistant genes. Four kinds of integron have been identified, and most clinical isolates bacilli have class I integron (31). So far, most integron types were found in *Enterobacteriaceae*, and the resistant gene box was the most complex. The main integron types were class 1, class 2 and class 3. Among them, class 1 and class 2 integron were reported more, and class 3 integron was only reported in a case (32,33). A lot of studies focused on the integron carried by infected patients, all class 1 integrons were found in clinical isolated strains. But there were many researchers detected integron in the environment out of the hospital

(34-37). We found that, 20 *Klebsiella pneumoniae* strains were integron positive, all of which were class I integron. The detection of integron in respiratory tract samples of lung cancer patients without pulmonary infection after chemotherapy is of great significance to detect the spread of drug resistance.

Conclusions

After chemotherapy for lung cancer patients, the bacteria isolated from respiratory tract were mainly gram-negative bacteria, with high resistance rate to common penicillin and cephalosporins. The detection rate of gram-positive bacteria was low, and the bacteria were highly resistant to penicillin. Fungi detection rate was high, and sensitive to common antifungal drugs. The clinical isolated strains carried class I integron, which can transmit resistant genes. Therefore, to guide the rational use of antibiotics, the drug sensitivity monitoring should be carried out in time for lung cancer patients with suspected pulmonary infection after chemotherapy. Integron positive bacteria has low toxicity and can survive in the human body for a long time, it can provide the possibility for the epidemic of infectious diseases once conditions are suitable. Therefore, for uninfected patients, it is necessary to detect the spread of drug resistance through the detection of integron.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/jtd-20-928>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-928>). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Fuyang People’s Hospital. All participants were competent to provide their consent.

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