Impact of antibiotic use before definitive concurrent chemoradiation in patients with locally advanced non-small cell lung cancer

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Research Article

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Abstract

**Purpose:** The study evaluated whether antibiotic treatment before chemoradiotherapy influenced outcomes in patients with locally advanced non-small cell lung cancer (LA-NSCLC).

**Methods:** The records of LA-NSCLC patients treated with chemoradiotherapy between 2010 and 2017 at xxx were retrospectively examined together with their antibiotic use (antibiotic type, duration of treatment, and time between discontinuation and chemoradiotherapy). The influence of antibiotics on progression-free survival (PFS) and overall survival (OS) was evaluated with Kaplan-Meier curves and univariate and multivariate Cox regression.

**Results:** Of 522 patients, 176 had received intravenous broad-spectrum antibiotics in the month before chemoradiotherapy. Antibiotic use was linked to both reduced PFS (7.9 vs. 13.4 mo, \( p<0.001 \)) and OS (20.4 vs. 25.3 mo, \( p=0.049 \)). Multivariate regression demonstrated that antibiotic treatment was an unfavorable independent prognostic factor for LA-NSCLC patients that received chemoradiotherapy (HR, 1.234; 95% CI, 1.019-1.494; \( p=0.031 \)). Prognosis was also influenced by the antibiotic type, length of treatment, and interval between discontinuation and start of chemoradiotherapy initiation. \( \beta \)-lactamase inhibitors were found to be the most harmful (median OS for \( \beta \)-lactamase inhibitors /Fluoroquinolones /Cephalosporins:16.5/19.9/25.9 mo, \( p=0.045 \)). Cutoff values for interval and duration calculated by the X-tile procedure showed that intervals of 7-16 days or durations \( \leq 6 \) days did not significantly affect OS relative to untreated patients (intervals: \( p=0.9 \), duration: \( p=0.93 \)).

**Conclusions:** Antibiotic treatment for longer than six days, especially with \( \beta \)-lactamase inhibitors, was associated with poor prognosis. Furthermore, delaying chemoradiotherapy for 7-16 days after antibiotic discontinuation may reduce these negative effects.

Introduction

Approximately one-third of non-small cell lung cancer (NSCLC) cases are diagnosed at a locally advanced (LA) stage(1). If the cancer is unresectable, it is usually treated with chemoradiotherapy(2).

TNM stage, PS score, gender, and weight loss are classic independent prognostic factors for these patients(3). Unfortunately, these factors do not fully explain patient-to-patient differences in prognosis. Many lung cancer patients are prone to infection due to immunosuppression and tumor compression, leading to some patients receiving antibiotic therapy. Several preclinical studies have found that the abundance and diversity of gut microbes influence the efficacy and toxicity of multiple antineoplastic therapies, suggesting that broad-spectrum antibiotics, which can dysregulate the gut microbiota, might influence the response to antineoplastic therapy(4–7). However, the applicability of these findings to humans requires further study.

Recent clinical studies have investigated the influence of antibiotics on patients’ responses to immune checkpoint inhibitors, finding that antibiotic use affects the efficacy of immunotherapy(8–11). In
addition, in head and neck cancer, antibiotics have been shown to negatively affect patients receiving concurrent chemoradiotherapy(12). However, approximately 85% of the patients had also received immunotherapy, possibly confounding the findings. Therefore, it remains unclear whether the use of antibiotics affects the efficacy of concurrent chemoradiotherapy, especially in lung cancer.

Several systematic reviews have shown that for patients receiving immunotherapy, the type of antibiotic, timing, and duration of treatment affected their survival(13, 14). However, both timing and duration of treatment have been defined differently in different studies. It is also not known whether these findings apply to patients receiving concurrent chemoradiotherapy.

Here, we investigated the influence of antibiotic therapy on survival outcomes in LA-NSCLC patients receiving concurrent chemoradiotherapy and identified the antibiotic treatment characteristics associated with poor prognosis.

We present the following article in accordance with the STROBE reporting checklist.

**Materials And Methods**

**Patients**

LA-NSCLC patients who had received concurrent chemoradiotherapy at xxx between 2010 and 2017 were identified from medical records. Cases with pathologically or cytologically confirmed stage III, unresectable, LA-NSCLC were eligible. The patients had received platinum-based antineoplastic drugs together with definitive radiation therapy and were generally in good condition with PS scores of 0–1. The inclusion criteria also included receiving or not receiving intravenous broad-spectrum antibiotic therapy within the month before chemoradiotherapy. Patients who received first-line immunotherapy were excluded.

This study was approved by the ethics review committee of XXX and individual consent for this retrospective analysis was waived.

**Treatment**

The patients had received three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). The target definitions and treatment planning were as follows: gross tumor volumes comprised the primary tumor and affected lymph nodes, described as those with a ≥ 1 cm short-axis diameter measured by CT or high-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET). The clinical tumor volume was defined as the primary tumor together with a margin of 0.6–0.8 cm and ipsilateral hilum and mediastinal nodal stations. Radiation therapy was started on the first day of chemotherapy with the most commonly prescribed dose for radical radiotherapy being 60–70 Gy (2 Gy per fraction). Regimens for concurrent chemotherapy include cisplatin + etoposide, paclitaxel + carboplatin, and pemetrexed + platinum (carboplatin or cisplatin)(15, 16).
Study variables

Demographic and clinical information, including age, sex, smoking history, histological type, PS score, radiotherapy dose, radiation pneumonia, and antibiotic use, was obtained. Details of antibiotic treatment, including antibiotic type, timing, and treatment duration, were also obtained.

Endpoint definition

OS was determined as the interval between therapy and all-cause death or final follow-up. PFS was calculated as the time from treatment to disease progression, death without progression, or final follow-up.

Statistical analysis

Clinico-pathological characteristics were summarized descriptively by percentage and relationships between them were determined with Fisher's exact or chi-square tests. Kaplan-Meier curves were used to determine PFS and OS, with comparisons using log-rank tests. Cox proportional hazard models were used for univariate and multivariate analyses, and hazard ratios (HR) and 95% confidence intervals (CI) were calculated. The cut-off values for antibiotic therapy duration and time between discontinuation and start of chemoradiotherapy were determined by the X-tile procedure(17). The forest plots were used for subgroup analysis. All p-values were two-sided and were considered significant at \( p < 0.05 \).

Results

Patients

In total, 522 consecutive LA-NSCLC patients who had received concurrent chemoradiotherapy were included. Of these, 176 had been treated with broad-spectrum antibiotics in the month before anti-cancer therapy. The most frequently used antibiotics were cephalosporins [55 (31.3%)], fluoroquinolone antibiotics [55 (31.3%)] and \( \beta \)-lactamase inhibitors (42 (23.9%)), with 22 patients receiving combination antibiotics. Patients were classified into antibiotic-treated and antibiotic-untreated groups, and their information is detailed in Table 1. The groups were balanced in terms of clinicopathological characteristics.

The effect of antibiotic treatment on patient survival

Prior antibiotic use was related to worse PFS (7.9 vs. 13.4 mo, \( p=0.00015 \)) and OS (20.43 vs. 25.3 mo, \( p=0.049 \) (Figure 1 a-b). Based on the different clinicopathological characteristics, we undertook a subgroup analysis of PFS and OS; the results were consistent with those of the whole-group analysis, with antibiotic treatment negatively influencing survival, and reduced OS and PFS were seen in most subgroups (Figure 2).
Univariate and multivariate analysis

Progression-free survival

Univariate analysis demonstrated that age (HR, 1.251; 95%CI, 1.049-1.493, \(p=0.013\)), histological type (HR, 1.232; 95%CI, 1.032-1.470, \(p=0.021\)), and antibiotic treatment (HR, 1.431; 95%CI, 1.188-1.725, \(p<0.001\)) were associated with survival outcomes. Inclusion of these factors in the multivariate analysis demonstrated that antibiotic treatment was an independent prognostic factor for LA-NSCLC patients receiving chemoradiotherapy (HR, 1.496; 95%CI, 1.236-1.810, \(p<0.001\)) (Table 2).

Overall survival

Univariate analysis indicated that age (HR, 1.288; 95%CI, 1.075-1.543, \(p=0.006\)), histological type (HR, 1.276; 95%CI, 1.065-1.529, \(p=0.008\)), and antibiotic use (HR, 1.209; 95%CI, 1.000-1.462, \(p=0.050\)) were linked to reduced OS and the multivariate analysis found antibiotic use to be an independent prognostic factor for OS (HR, 1.234; 95%CI, 1.019-1.494, \(p=0.031\)) (Table 2).

The influence of antibiotic type on patient survival

Survival outcomes

The effects of three commonly used antibiotics on patient survival were investigated. Kaplan-Meier curves showed that different antibiotic treatments before chemoradiotherapy affected OS differently: β-lactamase inhibitors, 16.5 mo; fluoroquinolones, 19.9 mo; cephalosporins, 25.9 mo (\(p=0.045\)) (Figure 1c).

Next, cutoff values of 6 and 13 days for the duration of antibiotic use were determined using X-tile, and patients were assigned to three groups using these values (short duration, \(\leq 6\) days; intermediate duration, 6-13 days; long duration: >13 days). Cut-off values for the interval between antibiotic discontinuation and chemoradiotherapy initiation were determined as 7 and 16 days, and patients were assigned to three groups (short interval, \(\leq 7\) days; intermediate interval, 7-16 days; long interval, >16 days) (Figure 3).

Kaplan-Meier curves showed that patients receiving short duration antibiotic treatments (median OS: 24.8 [20.0-29.6] mo) survived longer than those on intermediate (median OS: 20.0 [16.1-23.9] mo) and long duration antibiotics (median OS: 14.2 [7.0-21.4] mo) (\(p=0.00061\)) (Figure 1d). Intermediate intervals between antibiotic discontinuation and chemoradiotherapy were linked to longer OS: 7-16 days (median OS: 24.8 [20.0-29.6] mo) compared with \(\leq 7\) days (median OS: 16.4 [13.9-18.9] mo) and >16 days (median OS: 19.8 [16.1-23.5] mo) (\(p=0.00098\)) (Figure 1e).

The OS did not differ significantly between patients treated with a short course of antibiotics and those who did not receive antibiotics (\(p=0.93\)) (Figure 4a). In addition, survival outcomes did not differ between patients who received chemoradiotherapy between 7-16 days after antibiotic discontinuation and those who did not receive antibiotics (\(p=0.9\)) (Figure 4b).
Patients were assigned to different subgroups based on cut-off values for duration and interval. The >6-day duration subgroup had a higher risk of death compared with the ≤6-days duration subgroup (HR:1.408, 95%CI:1.032-1.920, p=0.031) (Figure 4c). Patients in the ≤7-day interval or >16-day interval subgroups also showed an increased risk of dying relative to patients in the 7-16-day interval subgroup (HR:1.447, 95%CI:1.061-1.972, p=0.019) (Figure 4d) while the duration >6 days/interval ≤7 days or >16 days group had the highest risk of death relative to the duration ≤6 days/interval 7-16 days group (HR:1.681, 95%CI:1.158-2.440, p=0.006) (Figure 4e).

Discussion

Long-term survival is usually poor for unresectable LA-NSCLC even after chemoradiotherapy, with individual differences in survival times. We have previously found that these patients are susceptible to infection and thus often receive antibiotics. The effects of these antibiotics on survival are unknown. Here, we found that prior antibiotic use adversely affected survival and the antibiotic type, length of use, and timing had significant effects.

Preclinical evidence has suggested that disruption of the microbiome enhances tumor growth and metastasis(18); this has also been reported for lung cancers(19). The microbiome also influences the effectiveness of chemotherapy, radiation therapy, and immunotherapy(20–22). Antibiotic treatment reduced treatment-induced responses in myeloid and T helper cells17, decreasing the efficacy of oxaliplatin and cyclophosphamide(5, 6). Similar adverse effects have been observed in mice(20, 23–25) where antibiotics given before radiotherapy reduced the therapeutic effects(26). Antibiotics also reduce the efficacy of immunotherapy(8, 9, 11, 27) as well as that of concurrent chemoradiotherapy(12). Here, even after adjustment for confounding factors, antibiotic use was an independent prognostic factor for LA-NSCLC with chemoradiotherapy. It has been found that antibiotics reduce peripheral blood lymphocytes in mice, resulting in persistent lymphocytopenia after chemoradiotherapy(28). Both OS and PFS were reduced in LA-NSCLC cases with persistent lymphopenia after chemoradiotherapy(29).

It is, however, not feasible to completely avoid antibiotic treatment in clinical practice. Therefore, it is important to minimize the negative effects of chemoradiotherapy. Analysis of the antibiotic type, together with timing and duration of treatment, showed that β-lactamase inhibitors were the most deleterious, followed by fluoroquinolones and cephalosporins. This confirms previous findings(27). Another study showed that β-lactamase inhibitors, but not other antibiotics, adversely affected OS in lung cancer cases treated with immune checkpoint inhibitors(30). This may be a consequence of the broader antimicrobial spectrum and relatively low resistance rate of β-lactamase inhibitors, which may affect beneficial bacteria. Fungi may also modulate the immune response in opposition to the bacterial microbiota(26). Therefore, we hypothesize that β-lactamase inhibitors may influence chemoradiotherapy efficacy not only by removing beneficial bacteria but also by amplifying fungi. This requires further investigation.

The time-dependent proliferation of gut microbes occurs after antibiotic discontinuation; however, in clinical practice, delaying antitumor therapy increases the risk of tumor progression. A study of 247
NSCLC and 121 renal carcinoma patients observed worse outcomes after antibiotic use in the month before immunotherapy, although the effect was reduced if the interval was extended to two months(31). Another study used a cut-off of 14 days, with decreased ORR and PFS(10). The use of shorter intervals (one and two weeks) between antibiotic discontinuation and chemoradiotherapy led to earlier progression and reduced OS and DSS(12). Our study included mainly patients who received antibiotics within the month before chemoradiotherapy and found lower OS and PFS in these patients. Subdivision of the patients showed that antibiotic use 7–16 days before chemoradiotherapy was associated with a better prognosis for patients than either 7 or over 16 days before chemoradiotherapy. It is possible that if the interval is too short, the microbiome cannot recover, while longer intervals lead to increased tumor progression. The OS did not differ significantly between patients on antibiotics 7–16 days before chemoradiotherapy and those without antibiotics. This is consistent with previous findings that not all patients who receive antibiotics have a poorer prognosis and that adverse effects are related to the timing of antibiotic use. We hypothesize that delaying chemoradiotherapy after antibiotic discontinuation will attenuate the adverse effects and that the duration of the delay is related to different tumor populations and anti-tumor treatment regimens.

We also showed the importance of antibiotic treatment duration on prognosis. We assigned patients to three groups, observing that the longer the antibiotic treatment, the worse the prognosis. Extended antibiotic use has been shown to reduce immunotherapy efficacy in lung cancer patients(32, 33). Also, multiple antibiotic courses were associated with a worse prognosis in patients receiving chemoradiotherapy(12). We found no significant difference in patient OS between antibiotic treatment < 6 days and no treatment. Similarly, it was reported that shorter durations (6 days) did not affect immunotherapy efficacy in NSCLC patients(34). Our results warrant further investigation to find the optimal balance between reducing the risk of true infection in cancer patients and protecting the gut microbiota, which may provide clinical practice guidelines for LA-NSCLC patients receiving chemoradiotherapy.

The timing and duration of antibiotic therapy are both linked to survival in LA-NSCLC. Here, patients who received antibiotics for > 6 days and chemoradiotherapy with an interval of ≤ 7 days or > 16 days had a 1.681-fold higher risk of death than those who received antibiotics for ≤ 7 days and concurrent chemoradiotherapy after 7–16 days. Our findings may thus provide a clinical practice reference for LA-NSCLC patients receiving concurrent chemoradiation, that is, for patients with a longer duration of antibiotic use, chemoradiation should be administered at least 7 days apart. Notably, our study also suggests that longer intervals are also deleterious due to the risk of tumor progression.

Before the PACIFIC study, cases with inoperable LA-NSCLC were treated with concurrent chemoradiotherapy, while the PACIFIC study demonstrated a survival benefit for those who did not progress after radical chemoradiotherapy for stage III NSCLC in treatment with Durvalumab. Immunotherapy has since been introduced into the management of these patients. There is substantial evidence demonstrating the adverse effects of antibiotics on immunotherapy efficacy, and our study showed that antibiotic treatment before chemoradiotherapy was an unfavorable prognostic factor for LA-
NSCLC patients. And antibiotics have been reported to decrease circulating lymphocytes, thus reducing tumor microenvironment immunity, which would affect the efficacy of immunotherapy in patients with LA-NSCLC. Therefore, for these patients, we recommend the careful use of prophylactic antibiotics.

The study has several limitations. As this was a single-center retrospective investigation, selection bias is inevitable and there is heterogeneity in follow-up and treatment. We did not analyze the reasons for prescribing antibiotics but a study demonstrated that antibiotics were an unfavorable prognostic factor regardless of the reason for prescribing(12). Longer-term antibiotic use suggests combinations of severe infections and we did not explore whether the severity of the infection influenced patient prognosis. However, all included patients had PS scores of 0 or 1, and none died from infection. We believe that antibiotic-induced lymphopenia influenced prognosis, but we did not further analyze and verify the changes in peripheral blood lymphocyte counts in patients before and after treatment. In addition, although we assessed the optimal timing and duration of antibiotic use by the X-tile procedure, we did not perform experiments and analyses of gut microbes to clarify the underlying mechanisms; this requires verification using prospective studies.

**Conclusions**

It was found that antibiotic use was an unfavorable prognostic factor in LA-NSCLC patients receiving concurrent chemoradiation and that this unfavorable effect increased significantly with cumulative antibiotic use. Delaying concurrent chemoradiation for 7 to 16 days after the end of antibiotic therapy may attenuate the adverse effects of antibiotics. In addition, β-lactamase inhibitors were found to have the most deleterious effects on prognosis, compared with other antibiotics. Therefore, in clinical practice, the indications for the use of this antibiotic should be strictly controlled and used with caution.

**Abbreviations**

- **LA-NSCLC**  Locally advanced non-small cell lung cancer
- **PFS**  Progression-free survival
- **OS**  Overall survival
- **3D-CRT**  Three-dimensional conformal radiotherapy
- **IMRT**  Intensity-modulated radiotherapy
- **FDG**  Fluorodeoxyglucose
- **PET**  Positron emission tomography
- **HR**  Hazard ratios
CI  Confidence intervals

Declarations

Ethics approval and consent to participate

This study was approved by the ethics review committee of West China Hospital, Sichuan University (IRB No.2021-1300) and individual consent for this retrospective analysis was waived.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This project was supported by a grant from ‘1,3,5’ distinguish development project of West China Hospital (ZYJC21075 to Youling Gong), Sichuan University.

Authors’ contributions

Youling Gong conceived and designed the study. Ting Mei, Xuexi Yang, and Min Yu collected the data. Ting Mei and Youling Gong analyzed and interpreted the data and drafted the article. Xiaoman Tian, Qianyue Deng, Xianyan Chen critically revised the paper. All of the authors approved the final submitted version.

Acknowledgements

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References


Tables
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Abbreviations: Abx, antibiotics
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Antibiotic

| Yes vs. No | 1.209 (1.000-1.462) | 0.050 | 1.234 (1.019-1.494) | 0.031 |

**Figures**

![Kaplan-Meier survival curves](image)

**Figure 1**

Kaplan-Meier survival curves

a. The effect of antibiotic treatment on PFS, b. The effect of antibiotic treatment on OS, c. The effects of different antibiotics on survival, d. The effects of different intervals on survival, e. The effects of different durations of antibiotic treatment on survival.
Figure 2

Forest plot for PFS (a) and OS (b)
Figure 3

X-tile analysis for overall survival

a-c. X-tile analysis based on interval time, d-f. X-tile analysis based on duration. X-tile plots are shown in the left panels; optimal cut-off values are indicated by black circles in the panel and are represented as histograms of the whole cohort in the middle panel; right panels show Kaplan-Meier curves.

Figure 4
Kaplan-Meier curves and cumulative hazard analysis for survival

Kaplan-Meier curves: a. No Abx vs. Duration \( \leq 6 \) days; b. No Abx vs. Intervals 7-16 days, Cumulative hazard analysis: c. Intervals 7-16 days vs. Other intervals; d. Duration \( \leq 6 \) days vs. Duration >6 days; e. Intervals 7-16 days/Duration \( \leq 6 \) days vs. Intervals 7-16 days/Duration >6 days vs. Other intervals/Duration \( \leq 6 \) days vs. Other intervals/Duration >6 days; 1: Intervals 7-16 days/Duration \( \leq 6 \) days; 2: Intervals 7-16 days/Duration >6 days; 3: Other intervals/Duration \( \leq 6 \) days; 4: Other intervals/Duration >6 days; Other intervals: intervals \( \leq 7 \) days or intervals >16 days.