Efficacy and safety of concurrent anti-tuberculosis treatment and chemotherapy in lung cancer patients with co-existent tuberculosis

Mei-Feng Ye[1#], Shan Su[2#], Zhi-Hao Huang[2#], Jian-Jun Zou[2], Duo-Hua Su[3], Xiao-Hui Chen[4], Long-Feng Zeng[3], Wei-Xiang Liao[3], Hui-Yi Huang[2], Yun-Yun Zeng[2], Wen-Chang Cen[2], Xian-Lan Zhang[2], Chun-Xin Liao[3], Jian Zhang[5], Yan-Bin Zhang[3]

[1]Guangzhou Medical University, Guangzhou, China; [2]Department of Oncology, Guangzhou Chest Hospital, Guangzhou, China; [3]Department of Tuberculosis, Guangzhou Chest Hospital, Guangzhou, China; [4]Department of Thoracic Surgery, Guangzhou Chest Hospital, Guangzhou, China; [5]Department of Oncology, Zhujiang Hospital, Guangzhou, China

Contributions: (I) Conception and design: S Su, YB Zhang; (II) Administrative support: YB Zhang, J Zhang; (III) Provision of study materials or patients: JJ Zou, DH Su, XH Chen, LF Zeng, WX Liao, HY Huang, YY Zeng, WC Cen, XL Zhang, CX Liao; (IV) Collection and assembly of data: ZH Huang, MF Ye; (V) Data analysis and interpretation: S Su, MF Ye; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Prof. Yan-Bin Zhang. Guangzhou Chest Hospital, 62 Hengzhigang Rd., Guangzhou, China. Email: drzhangyb@hotmail.com; Prof. Jian Zhang. Zhujiang Hospital, 253 Gongye Rd., Guangzhou, China. Email: blacktiger@139.com.

Background: This retrospective study evaluated the safety and efficacy of concurrent anti-tuberculosis (TB) and chemotherapy treatment in patients with advanced lung cancer and active TB.

Methods: We retrospectively analyzed patients who were first diagnosed with advanced lung cancer and received first-line chemotherapy in Guangzhou Chest Hospital from 2015 to 2017. Patients were categorized into two groups (2:1): lung cancer patients without active TB (Group A), and lung cancer patients with active TB (Group B). Primary endpoints included adverse events (AEs), objective response rate (ORR), time to treatment failure, and overall survival (OS).

Results: A total of 99 patients were eligible (Group A, n=66; Group B, n=33). Grade ≥3 treatment-related AEs, primarily hematologic toxicity, occurred in 39.4% and 51.5% of patients in Groups A and B, respectively. The hypohepatia in both groups was generally at grade 1 or 2, with similar incidences (26% and 27%, respectively). After two cycles of chemotherapy, the ORR was 42.4% and 33.3% in Group A and B, respectively (P=0.383). The median time to treatment failure (TTF) was 7.0 and 5.6 months for Groups A and B, respectively (P=0.175). The median OS was 17.0 and 14.0 months for Groups A and B, respectively (P=0.312). After 3 months of anti-TB treatment, all patients achieved sputum acid-fast bacilli (AFB) smear conversion and absorption on imaging, and the end of follow-up observed no recurrence.

Conclusions: Concurrent anti-TB and chemotherapy treatment did not increase hematological toxicity or hypohepatia in lung cancer patients with pulmonary TB.

Keywords: Lung cancer; pulmonary tuberculosis (pulmonary TB); chemotherapy

Introduction

Lung cancer with tuberculosis (TB) was first reported in the 19C. Since then, extensive research has been conducted on the co-existence of these two diseases. Immunodeficiency due to lung cancer treatment can cause the reactivation of TB, while TB increases lung cancer risk due to confounding factors (1-3). Data from Japan from the last twenty years estimates that 1–2% of lung cancer patients have active TB (4,5). The incidence may be higher in countries with a higher TB burden.

Anti-TB drugs, such as isoniazid and rifampicin, can cause a decline in white blood cells and platelets, and damage liver function, which are also common adverse effects of chemotherapy (6-8). Most previous studies have been limited to the epidemiology of co-existent TB and lung cancer and the relationship between them. Few studies have examined the efficacy and safety of concurrent chemotherapy and anti-TB treatment. A South Korean study found that anti-cancer chemotherapy is not an obstacle to treating TB (9). A study from Japan focused on patients with malignancy, and active TB suggested that concurrent chemotherapy and anti-TB treatment is effective and safe (10). However, due to the small sample size, the diversity of tumor types, and lack of controls, there are few evidence-based recommendations for combination treatment. China, one of the top 30 countries globally in terms of TB burden, has a consistently high incidence of lung cancer (11). Thus, it is of particular importance to China to determine the optimal strategy for treating lung cancer patients with co-existent TB, and beneficial for other areas where both TB and lung cancer are prevalent.

The present study explored the efficacy and safety of concurrent chemotherapy and anti-TB treatment in lung cancer patients with active TB in China. The clinical outcomes of these patients were also explored.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5964).

Methods

Study population

We retrospectively analyzed patients who were first diagnosed with advanced lung cancer and received first-line chemotherapy in Guangzhou Chest Hospital from 2015 to 2017. For patients records retrieved from hospital electronic medical record system, data included age, gender,

tuberculosis diagnosis, tumor stage, pathological type, adverse events, treatment information (include anti-TB treatment and chemotherapy), and survival data. Patients with stage I–III cancer, positive driver gene mutations (*EGFR*, *ALK*, or *ROS1*), multiple chemotherapies, or absence of treatment information was excluded. Ninety-nine eligible patients were identified and propensity score matched into two groups (2:1): patients without co-existence of active pulmonary TB (Group A; n=66) and patients with co-existence of active pulmonary TB (Group B; n=33) (*Figure 1*). Variables used for propensity matching were as follows: age, sex, smoking history, ECOG performance status, disease stage and pathology. Patient characteristics at the baseline are summarized in *Table 1*.

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Guangzhou Chest Hospital (No. 2020-21). The requirement of informed consent was waived because of the retrospective nature of the study.

Diagnosis of TB

Active pulmonary TB was diagnosed in several ways:

Positive smear test for acid-fast bacilli (AFB) in sputum specimen or bronchial washing. In smear-negative specimens, a follow-on test of mycobacteria using a WHO-approved rapid diagnostic reagent, e.g., Xpert MTB/RIF, was performed.

Pathological diagnosis of granulomatous inflammation obtained by bronchoscopy or percutaneous lung biopsy (PTLB).

For patients who could not be diagnosed by microbiology or pathology, pulmonary TB was diagnosed based on typical pulmonary TB clinical symptoms, manifestations on chest X-ray, and effectiveness of anti-TB treatment after excluding other pulmonary diseases.

Procedures

Chemotherapy regimens for different pathological types of lung cancer are shown in *Table 2*. Regimens and pathology types were well-balanced between the two groups. Most patients received 21-day cycles of first-line platinum-based chemotherapy, including pemetrexed, paclitaxel, etoposide, and gemcitabine. One patient in each group received a 28-day cycle of oral tegafur monotherapy due to poor physical condition (ECOG performance status =3).
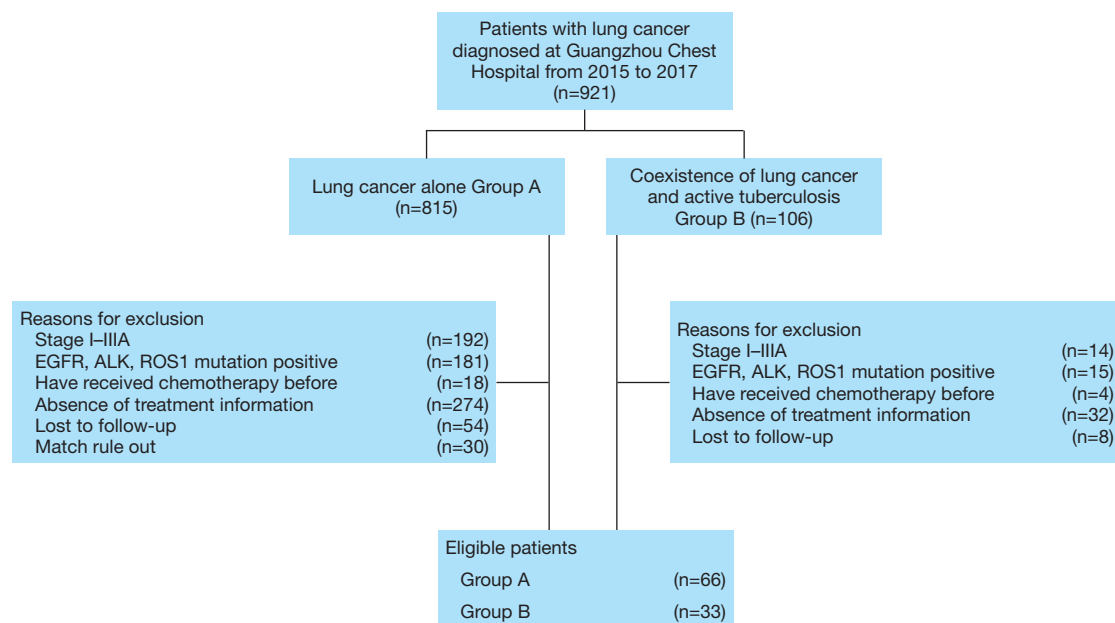
Figure 1 Flow chart of patient eligibility.

Patients with active TB (Group B) initially received a rifampicin-based anti-TB treatment regimen, including isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). All patients received 2–3 months of intensive treatment and 4–6 months of consolidation treatment.

Evaluation of efficacy and safety

Chest computed tomography (CT) was carried out every two chemotherapy cycles to determine tumor response and disease progression. Short-term efficacy was evaluated based on tumor response, classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (12). Objective response rate (ORR) was the percentage of patients with CR and PR. Disease control rate (DCR) was the percentage of patients with CR, PR, and SD. Time to treatment failure (TTF) was defined as the time from initiation of chemotherapy until discontinuation of first-line chemotherapy due to PD, therapeutic toxicity, patient preference, or death. Overall survival (OS) was defined as the interval from pathological diagnosis to death for any reason. Patients who survived or who were lost to follow-up were censored at the time of the last follow-up.

Safety was measured by comparing the incidence of treatment-related adverse events (AEs) in each group. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

Statistical analysis

Differences in demographics, clinicopathological characteristics, AEs, and ORR were assessed using the Chi-squared or Fisher's exact tests. TTF and OS were evaluated by the Kaplan-Meier method and compared with results generated using the log-rank test. Statistical analyses were performed using SPSS version 22.0. All reported P values were two-tailed, and differences were considered statistically significant at $P<0.05$.

Results

Efficacy of anti-TB treatment

Of the 33 patients in Group B, ten started chemotherapy within 2 weeks of anti-TB treatment, and 23 received chemotherapy after 2 weeks of anti-TB treatment. After 3 months of anti-TB treatment, all patients achieved sputum AFB smear conversion and absorption on imaging. The end of follow-up observed no recurrence.

Page 4 of 9

Ye et al. Evaluation of concurrent chemotherapy and anti-tuberculosis therapy

Table 1 Demographics and baseline patient characteristics

Characteristic	Group A (n=66), n [%]	Group B (n=33), n [%]	P
Age, years			0.887
Median	60	60	
Range	44–80	40–80	
<60	33 [50]	16 [48]	
≥60	33 [50]	17 [52]	
Sex			0.074
Male	54 [82]	32 [97]	
Female	12 [18]	1 [3]	
Smoking history			0.494
Yes	50 [76]	27 [82]	
No	16 [24]	6 [18]	
ECOG PS			0.867
0–1	52 [78.8]	25 [75.8]	
2	13 [19.7]	7 [21.2]	
3	1 [1.5]	1 [3.0]	
4	0	0	
Disease stage			0.744
IIIB	16 [24]	9 [27]	
IV	50 [76]	24 [73]	
Pathology			0.932
Adenocarcinoma	32 [49]	17 [51]	
Squamous-cell carcinoma	20 [30]	10 [30]	
SCLC	14 [21]	6 [19]	

SCLC, small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy of chemotherapy

Three patients were excluded from analysis due to a lack of assessment data. The efficacy of chemotherapy was evaluated in the remaining 96 patients (*Table 3*). ORRs were 42.4% (28 patients) and 33.3% (11 patients) in Group A and Group B, respectively (P=0.383). DCRs in either group were not statistically different (81.8% *vs.* 72.7% in Group A and B respectively; P=0.297), irrespective of pathology type, age, sex, smoking status, or ECOG performance status.

At the cutoff date of March 1, 2019, seven patients (10.6%) in Group A remained on anti-tumor treatment, three patients (4.5%) had discontinued treatment due to AEs, and 52 (78.8%) patients had discontinued treatment

due to disease progression.

In Group B, 27 patients (82%) had discontinued therapy due to disease progression, and one patient had discontinued treatment due to grade 3 neutropenia and grade 4 thrombocytopenia.

Patients in Group A had a similar treatment time to Group B (median TTF 7.0 *vs.* 5.6 months, respectively; HR, 0.74; 95% CI, 0.45–1.19; P=0.175) (*Figure 2A*). We conducted an exploratory subgroup analysis of the TTF review according to pre-specified baseline characteristics; the results were generally consistent with the overall population (*Figure 2B*).

At the cutoff date of March 1, 2019, 46 patients (69.7%)

Table 2 Chemotherapy regimens for different pathological types of lung cancer

Regimens	Group A (n=66), n (%)	Group B (n=33), n (%)	P
Adenocarcinoma	32	17	0.144
GEM + DDP	1 (3.1)	2 (11.8)	
PEM + DDP	28 (87.6)	11 (64.7)	
PTX + DDP	2 (6.3)	4 (23.5)	
S1	1 (3.1)	0	
Squamous-cell carcinoma	20	10	0.164
PTX + DDP	15 (75.0)	5 (50.0)	
GEM + DDP	5 (25.0)	3 (30.0)	
VP-16 + DDP	0	1 (10.0)	
S1	0	1 (10.0)	
SCLC	14	6	0.587
VP-16 + DDP	12 (85.7)	5 (83.3)	
IPI + PLAT	1 (7.1)	1 (16.7)	
PTX + DDP	1 (7.1)	0	

GEM, gemcitabine; PEM, pemetrexed; PTX, paclitaxel; DDP, Cisplatin; S1, tegafur; SCLC, small cell lung cancer; VP-16, Etoposide; IPI, irinotecan.

**Table 3** Tumor response rates after two chemotherapy cycles

Tumor response rates	Group A (n=66), n (%)	Group B (n=33), n (%)	P
CR	1 (1.5)	0	
PR	27 (40.9)	11 (33.3)	
SD	26 (39.4)	13 (39.4)	
PD	10 (15.2)	8 (24.3)	
Not evaluable/not applicable	2 (3.0)	1 (3.0)	
ORR (CR + PR)	28 (42.4)	11 (33.3)	0.383
DCR (CR + PR + SD)	54 (81.8)	24 (72.7)	0.297

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

in Group A and 28 (84.8%) in Group B had died. The median duration of follow-up for OS was 8 and 6 months in Group A and B, respectively. Median OS in Group A was 17 months (95% CI, 9.7–24.3 months) and in Group B was 14 months (95% CI, 10.5–17.5 months) with no statistically significant difference in OS (HR, 0.76; 95% CI, 0.44–1.33; P=0.312) (*Figure 2C*). In the univariate analysis, age, performance status, smoking status, and pathology were not significantly associated with OS (*Figure 2D*).

Safety of concurrent anti-TB treatment and chemotherapy

The incidence of AEs of any cause was 84.8% (56/66) in Group A and 97% (32/33) in Group B (*Table 4*). In Group A, the most frequently reported AEs of any grade were anemia (69.7%), neutropenia (53.0%), thrombocytopenia (24.2%), and hypohepatia (25.8%) and in Group B, anemia (81.8%), neutropenia (54.6%), thrombocytopenia (18.2%), and hypohepatia (27.3%). The frequency of grade ≥3 treatment-related AEs of any cause was similar in both groups (39.4%
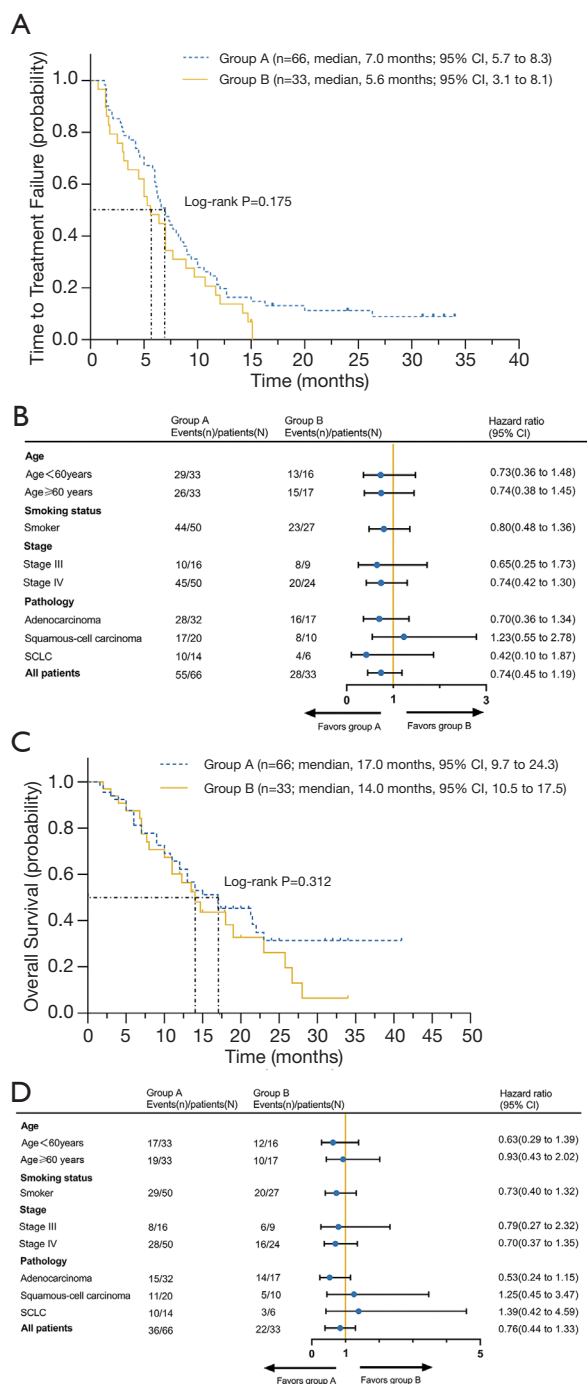
Figure 2 (A) Kaplan-Meier curve of TTF. (B) Forest plot depicting exploratory subgroup analyses effect on TTF. (C) Kaplan-Meier curve of OS. (D) Forest plot depicting exploratory subgroup analyses effect on OS (Group A vs. Group B). OS, overall survival; TTF, time to treatment failure.

and 51.5% in Group A and B, respectively). Among these, the most common grade ≥3 treatment-related AEs were hematologic toxicity, including comprised neutropenia (25.8% vs. 24.2% in Groups A and B, respectively; P=0.87) and anemia (24.2% vs. 33.3% in Groups A and B, respectively; P=0.338). Only one case with grade ≥3 hypohepatia occurred in Group B. In subgroup analysis, a higher incidence of anemia was observed in patients over 60 years of age in Group B (see *Table S1*). There was no significant difference in the incidence of AEs between the subgroups based on the baseline characteristics.

Four patients in each group received a reduced chemotherapy dose due to grade ≥3 neutropenia. One patient in Group A and three patients in Group B received blood transfusions for grade 3 anemia. One patient in Group B discontinued chemotherapy and changed the anti-TB regimen due to grade 3 hypohepatia. No treatment-related AE deaths occurred in either group.

Discussion

Three main theories exist for the co-existence of lung cancer and TB: anti-cancer therapy can cause reactivation of TB; TB is a predisposing factor for lung cancer; or, it is random (13,14). However, there is no standard treatment regimen for lung cancer patients with TB. The present study aimed to demonstrate the efficacy and safety of concurrent chemotherapy and anti-TB treatment. Our retrospective analysis revealed that anti-TB treatment in patients with co-existent TB and lung cancer did not affect chemotherapy efficacy and effectively controlled TB. Furthermore, the incidence of AEs in these patients did not increase. To the best of our knowledge, this is the first study with a large sample size to compare the efficacy and safety of concurrent anti-TB treatment and chemotherapy versus chemotherapy alone.

Several previous studies have focused on the efficacy and AEs of concurrent chemotherapy and anti-TB treatment in cancer patients with active TB. Kim *et al.* observed that chemotherapy did not affect the outcome of TB treatment, based on 24 lung cancer patients with co-existing TB (9). Hirashima *et al.* analyzed 30 metastatic colorectal cancer patients with *Mycobacterium tuberculosis* (MTB) or *Mycobacterium kansasii* (MK) infection. They found that it was safe and effective for patients to undergo chemotherapy

Table 4 Treatment-related AEs reported in Group A and Group B patients

Adverse event	Group A (n=66), n (%)			Group B (n=33), n (%)		
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4
Any adverse event	30 (45.6)	17 (25.8)	9 (13.6)	15 (45.5)	14 (42.4)	3 (9.1)
Neutropenia	18 (27.3)	9 (13.6)	8 (12.1)	10 (30.3)	6 (18.2)	2 (6.1)
Anemia	30 (45.6)	16 (24.2)	0	16 (48.5)	11 (33.3)	0
Thrombocytopenia	14 (21.2)	1 (1.5)	1 (1.5)	5 (15.2)	0	1 (3.0)
Hypohepatia	17 (25.8)	0	0	8 (24.2)	1 (3.0)	0

AEs, adverse events.

after some time following MTB or MK treatment (15). They performed another retrospective analysis of 30 patients with various solid cancers and co-existing MTB infection, including eight lung cancer patients, and the results showed that combination therapy was safe and feasible (10). Nevertheless, given the small sample sizes, the differing histories of anti-tumor therapy, and the various cancer types, the conclusions reached in these studies warranted further investigation. In the present study, we enrolled treatment-naïve patients who were diagnosed with lung cancer alone or lung cancer with co-existent active TB and confirmed the safety and effectiveness of the anti-TB treatment combined with chemotherapy. However, little evidence exists on the optimum initiation time for chemotherapy following anti-TB therapy. It has been reported that sputum bacteria turned negative after 2–4 weeks of anti-TB treatment (16), which appears to be the appropriate time to start chemotherapy. But according to our previous clinical practice, chemotherapy has little impact on immunity for patients with solid tumors, and concurrent chemotherapy and tuberculosis treatment seem to be safe and feasible. So in this study, some patients started chemotherapy and anti-TB treatment simultaneously, while others started chemotherapy after 2 weeks of anti-TB treatment. All of these patients achieved sputum conversion and radiographic remission after 3 months of anti-TB therapy. This result suggests that anti-TB treatment concurrent with chemotherapy may be a feasible strategy, but additional large-scale studies are warranted.

Due to hepatic microsomal drug-metabolizing enzymes, drug-induced hypohepatia is one of the most common AEs of both anti-TB treatment and chemotherapy (17,18). Although no increased incidence of drug-induced hypohepatia was observed in patients with concurrent chemotherapy and anti-TB therapy. Drug

interactions cannot be ignored. Isoniazid inhibits hepatic enzymes, which can delay metabolism and increase the concentration of drugs (17). Conversely, rifampicin induces hepatic enzymes, which can accelerate drug metabolism and reduce plasma drug concentrations, especially for tyrosine kinase inhibitors such as gefitinib and erlotinib (19,20). In this study, patients with a driver gene mutation were excluded. However, in clinical practice, EGFR-mutant lung cancer patients sometimes exhibit co-existent active TB. The incidence of grade 3 hypohepatia caused by EGFR-TKIs has been reported to be approximately 1.7–18% (21). However, there is little information on the AEs of EGFR inhibitors combined with anti-TB treatment. Rifampin should be excluded from anti-TB treatment in EGFR-mutant lung cancer patients considering drug metabolism and potential interactions. An alternative strategy is to use compounds metabolized by bile, such as afatinib (22). Polymorphisms in genes encoding hepatic drug-metabolizing enzymes may be related to hypohepatia caused by some drugs (23,24). In the future, it will be possible to create individualized therapies at the genetic level that avoid drug-induced hypohepatia.

Presently, chemotherapy, targeted therapies, and immunotherapy are the mainstays of treatment for advanced non-small-cell lung cancer. Cell-mediated immunity plays a vital role in the development of TB. It has been reported that MTB promotes tumor metastasis by inhibiting the T-cell immune response through the PD-1/PD-L1 pathway (25). However, whether immune surveillance is involved in the development of TB remains unclear. Fujita *et al.* reported the appearance of TB in a lung cancer patient during PD-1 inhibitor treatment (26), but none of the patients in our study received PD-1 inhibitor treatment. Therefore, results suggested that the efficacy of immunotherapy combined with anti-TB treatment in lung

cancer patients with co-existent active TB requires further investigation.

There were limitations to our study. First, although propensity score matching has been used to minimize confounding bias, the potential selective bias emanated from the retrospective nature of research cannot be avoided completely. Second, we did not test for the hepatitis B virus (HBV), a common infection in China. The conclusions in this subgroup may be different. Thirdly, subgroup analysis was not performed in patients with drug-resistant TB, diabetes, or other autoimmune diseases whose anti-TB treatment was unusual. Thus, our conclusions may not apply to these patients. Additionally, due to the sample size, our study only focused on advanced lung cancer patients receiving first-line chemotherapy. The impact of multiple lines of chemotherapy and HBV infection were not analyzed. Finally, since only one patient with co-existent TB and lung cancer changed the anti-TB regimen, our study was unable to evaluate whether the adjustment of anti-TB regimen would affect the results of the study.

In conclusion, this study revealed that concurrent first-line chemotherapy and anti-TB treatment in lung cancer patients with co-existent TB did not increase the incidence of AEs such as hypohepatia and hematologic toxicity, and did not affect the efficacy of either the anti-TB therapy or chemotherapy.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-5964

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-5964). 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Guangzhou Chest Hospital (No. 2020-21). The requirement of informed consent was waived because of the retrospective nature of the study.

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Table S1 Subgroup analysis of treatment-related AEs in groups A and B

Characteristic	Group A (n=66)				Group B (n=33)			
	Neutropenia	Anemia	Thrombocytopenia	Hypohepatia	Neutropenia	Anemia	Thrombocytopenia	Hypohepatia
Age, years								
<60	14 (42.4%)	27 (81.8%)	9 (27.3%)	10 (30.3%)	9 (56.3%)	12 (75.0%)	3 (18.8%)	5 (31.3%)
≥60	21 (63.6%)	19 (57.6%)	7 (21.2%)	7 (21.2%)	9 (52.9%)	15 (88.2%)	3 (17.6%)	4 (23.5%)
Smoking status								
Smoker	28 (56.0%)	34 (68%)	15 (30.0%)	14 (28.0%)	15 (55.6%)	21 (77.8%)	5 (18.5%)	7 (25.9%)
Stage								
III	8 (50.0%)	13 (81.3%)	3 (18.8%)	1 (6.3%)	7 (77.8%)	9 (100%)	2 (22.2%)	2 (22.2%)
IV	27 (54.0%)	33 (66.0%)	13 (26.0%)	16 (32.0%)	11 (45.8%)	18 (75.0%)	4 (16.6%)	7 (29.2%)
Pathology								
Adenocarcinoma	12 (37.5%)	21 (65.6%)	5 (15.6%)	10 (31.3%)	7 (41.2%)	13 (76.6%)	3 (17.6%)	6 (35.3%)
Squamous-cell carcinoma	13 (65.0%)	17 (85.0%)	6 (30.0%)	4 (20.0%)	5 (50.0%)	9 (90.0%)	2 (20.0%)	2 (20.0%)
SCLC	10 (71.4%)	8 (57.1%)	5 (35.7%)	3 (21.4%)	5 (83.3%)	5 (83.3%)	1 (16.7%)	1 (16.7%)

AEs, adverse events; SCLC, small cell lung cancer.