

ARTICLE

Outcomes of concurrent versus sequential icotinib therapy and chemotherapy in advanced non-small cell lung cancer with sensitive EGFR mutations

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Abstract

To explore a better treatment strategy for patients with advanced non-small cell lung cancer harboring sensitive epidermal growth factor receptor mutations, a total of 271 patients were retrospectively analyzed. The patients were divided into two groups: the combination group (58 cases), which received concurrent icotinib, pemetrexed, and platinum treatment, and the sequential group (213 cases), which received the sequential pemetrexed and platinum therapy, followed by icotinib treatment. The primary end points were progression-free survival (PFS) and PFS on the subsequent line of therapy (PFS2). PFS in the combination group was significantly higher compared with that in the sequential group (16.89 months vs. 9.90 months; $p < 0.001$). PFS in the combination group was also significantly higher than PFS2 in the sequential group (16.89 months vs. 14.05 months; $p = 0.009$). The overall survival (OS) of the patients was 33.22 months (95% confidence interval (CI): 26.99–37.01) in the combination group and 26.47 months (95% CI: 25.05–26.95) in the sequential group ($p < 0.001$). The combination group's objective response rate was superior to that of the sequential group (79.31% vs. 52.11%; $p < 0.001$). Propensity score matching also revealed that icotinib therapy combined with chemotherapy extended the PFS, PFS2, and OS of the patients ($p < 0.0001$, $p = 0.003$, and $p = 0.001$, respectively). The combination group's objective response rate was also better compared with the sequential group (79.31% vs. 51.72%; $p = 0.001$). In conclusion, our study demonstrated icotinib combined with chemotherapy can improve survival efficacy better than the separated two-line therapy.

Study Highlights**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

For advanced non-small cell lung cancer (NSCLC) harboring activating EGFR mutants, EGFR-tyrosine kinase inhibitors (TKIs) are the standard first-line treatment. Unfortunately, most patients with NSCLC harboring EGFR mutations acquire EGFR-TKI resistance after EGFR-TKI treatment for about 10–14 months. Studies have indicated that chemotherapy plus EGFR-TKIs may have combined effects on the growth

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of NSCLC cells. However, until now, there has been no study comparing the concurrent and sequential EGFR-TKIs plus chemotherapy.

WHAT QUESTION DID THIS STUDY ADDRESS?

We retrospectively analyzed the efficacy and safety of concurrent versus sequential icotinib and chemotherapy in untreated NSCLC with sensitive EGFR mutations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

In the patients with NSCLC with sensitive EGFR mutations, the first-line pemetrexed plus platinum combined with icotinib better improved PFS, PFS2, and objective response rate compared with first-line icotinib and second-line pemetrexed plus platinum.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The results of this paper provide guidance for the strategy choice in the treatment of patients with NSCLC.

INTRODUCTION

Lung cancer is the most common malignancy and the leading cause of cancer-related death worldwide.¹ Due to misdiagnosis and the absence of symptoms and efficient thoracic computed tomography scanning in the early stages, most lung cancers are diagnosed in the advanced stages.² Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancers, and lung adenocarcinoma is the most common pathological NSCLC subtype.³ EGFR activating mutations are present in 10–15% of patients with lung adenocarcinoma in North America and ~60% of Asian patients.^{4,5} The emergence of EGFR tyrosine kinase inhibitors (EGFR-TKIs) has provided a new treatment option with an improved response relative to previously available treatment options. For advanced NSCLC harboring activating EGFR mutants, EGFR-TKIs represent the standard first-line treatment.⁶

However, most patients with NSCLC harboring EGFR mutations acquire EGFR-TKI resistance after EGFR-TKI treatment for about 10–14 months. In the past decade, several studies have explored new treatment strategies to improve the survival of patients with lung cancer. The results of *in vitro* studies have indicated chemotherapy plus EGFR-TKIs may have combined effects on the growth of NSCLC cells.^{7,8} A study from Japan revealed that first-line chemotherapy combined with EGFR-TKIs can improve the survival of patients with EGFR-mutated lung adenocarcinoma.⁹ A recent study also reported that gefitinib plus chemotherapy as first-line therapy can offer longer progression-free survival (PFS) and overall survival (OS) than gefitinib or chemotherapy alone for patients with EGFR-mutant lung adenocarcinoma.¹⁰ In addition, several ongoing phase III trials are comparing EGFR-TKI with EGFR-TKI plus platinum-based chemotherapy as first-line treatment.¹¹ However, until now, no study has compared concurrent and sequential EGFR-TKI therapy with chemotherapy.

The different types of TKIs have the same mechanism of action, as they all block EGFR kinase activity by competing with adenosine triphosphate for EGFR binding sites. At

present, there are mainly three generations of EGFR-TKI on the market: gefitinib, erlotinib, and icotinib. In the first-line treatment of patients with advanced NSCLC, erlotinib has certain advantages over gefitinib. In a comparative multicenter retrospective study of gefitinib and erlotinib in Taiwan, 1,122 patients were enrolled, of which 407 were in the erlotinib group and 715 were in the gefitinib group.¹² The study demonstrated that the erlotinib group survived better than the gefitinib group. The disease control rates of the erlotinib group and gefitinib group were 65.8% and 58.9%, respectively ($p = 0.025$); the median PFS of the erlotinib group and gefitinib group was 4.6 and 3.6 months, respectively ($p = 0.027$); and the median OS of the erlotinib group and gefitinib group was 10.7 and 9.6 months, respectively ($p = 0.013$).¹² Icotinib is currently less researched in this area. In a phase III clinical double-blind controlled trial (ICOG trial) of icotinib and gefitinib, icotinib was not inferior to gefitinib concerning PFS, OS, and objective response rate (ORR).¹³

In this study, we retrospectively analyzed the efficacy and safety of concurrent versus sequential icotinib therapy and chemotherapy in untreated patients with NSCLC who had sensitive EGFR mutations to provide guidance for the strategy choice in the treatment of patients with NSCLC.

MATERIALS AND METHODS

Patients

This retrospective study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University, China, and was performed based on the Helsinki Declaration (as revised in Fortaleza, October 2013). All the patients signed written informed consent before participating in the study.

A total of 584 patients with stage IIIB/IV NSCLC receiving icotinib and pemetrexed plus platinum in the Affiliated

Hospital of Qingdao University from January 2015 to December 2017 were retrospectively analyzed. Before the analysis, the patient's records were anonymized. Based on the inclusion and exclusion criteria listed below, 271 patients were selected for this study. The patients were divided into two groups based on their treatment—the combination group (58 cases) and the sequential group (213 cases). Patients in the combination group were given first-line pemetrexed (500 mg/m², day 1) and platinum (carboplatin area under the curve [AUC] = 5, day 1) combined with icotinib (125 mg, t.i.d., p.o.). This treatment was repeated every 3 weeks for up to 6 cycles. Then, the patients were maintained with pemetrexed (500 mg/m², day 1) and icotinib (125 mg, t.i.d., p.o.) until unacceptable toxicity or disease progression or death occurred. Patients in the sequential group received first-line icotinib (125 mg, t.i.d., p.o.) until progressive disease (PD, namely PD1) developed, followed by second-line chemotherapy (pemetrexed [500 mg/m², day 1] and carboplatin [AUC = 5, day 1] and pemetrexed (500 mg/m², day 1) maintenance therapy until unacceptable progression (namely PD2) or toxicity or death occurred.

Inclusion criteria were patients pathologically diagnosed with advanced NSCLC (stage IIIB/IV), patients with sensitive EGFR mutations (exon 21 L858R or exon 19 deletions) confirmed by genetic testing, patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤2, patients with the eligible disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), and patients with available follow-up data.

Exclusion criteria were patients who received concurrent antitumor therapy, patients who had other cancers, and patients with EGFR T790M mutation-positive NSCLC after first-line icotinib therapy.

Data collection

We reviewed the electronic medical records of the patients and obtained their demographic information and clinical data—including, age, sex, disease stage, smoking status, ECOG PS, EGFR mutation status, efficacy, toxicity, clinical response, and survival data.

Outcome measurement

The primary end points of this study were PFS and PFS2. PFS was defined as the time interval from the date of diagnosis to the date of first-time disease progression. PFS2 in the sequential group was defined as the time interval from the date of second-line pemetrexed and platinum chemotherapy to the date of unacceptable progression. Secondary end points included OS, ORR, disease control

rate, and adverse events. Tumor response from the baseline was assessed based on the results of computed tomography with RECIST every 2 cycles or 2 months. Therapeutic evaluations were performed according to the RECIST criteria (version 1.1) and classified as complete response (CR; the disappearance of all target lesions), partial response (PR; at least 30% decrease in the sum of the longest diameter of target lesions taking the baseline sum longest diameter as reference), stable disease (neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, with the smallest sum of longest diameter since the beginning of the treatment as a reference), and PD (at least 20% increase in the sum of target lesions, taking the smallest sum on the study as a reference). (In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm; the appearance of one or more new lesions is also considered the progression.)

The ORR comprised CR and PR. The disease control rate was defined as CR, PR, and stable disease. Adverse events were graded according to the National Cancer Institute toxicity classification standard version 4.0. The radiological evaluation was performed by two independent oncologists. Generally, the first evaluation was performed 1 month after initiating therapy, and then assessment was conducted every 2 cycles or 2 months or at the progression of an original symptom.

Statistical analysis

All statistical analyses were performed using the SPSS version 24.0 software for Windows (IBM, Armonk, NY). Continuous variables were described as the mean ± standard deviation, whereas categorical variables were reported as numbers (percentages). Associations between clinical elements and survival were evaluated by univariate analysis using the log rank test. The multivariate Cox regression model was used to calculate the hazard ratios. The χ^2 test or Fisher's exact test was performed to compare the differences of ORRs between the two groups. Survival probability was analyzed using the Kaplan–Meier method.

Propensity match analysis was used to reduce the influence of confounding factors and the preference of patient's choice on the results. Logistic regression was used to calculate the propensity scores of confounding factors, such as age, sex, ECOG, clinical tumor-node-metastasis stage (and the existence of brain metastasis), EGFR mutation status, and smoking. According to the principle of similar propensity scores, nonrepeated matching grouping was performed. After the pairing was completed, the survival differences between the two groups were analyzed. A p value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The demographics and baseline disease characteristics of the patients are shown in Table 1. A total of 58 patients (21.40%) in the combination group received first-line therapy of pemetrexed and platinum combined with icotinib, whereas 213 patients (78.60%) in the sequential group received first-line icotinib therapy, followed by second-line pemetrexed and platinum therapy after disease progression. The average age of the patients was 61.8 years, ranging from 40 to 79 years. In addition, among the patients, 181 (66.79%) were women, 93 (34.32%) were over 65 years old, 67 (24.70%) were current or former smokers, 243 (89.67%) had ECOG PS of 0 or 1, 139 (51.29%) had deletions in exon 19, whereas 207 (76.38%) were in stage IV of NSCLC. Notably, 124 patients in the sequential group were with T790M mutation-negative status, whereas 89 patients did not have T790M mutation assay after icotinib resistance. In the combination group, 21 patients had a T790M mutation-positive status, 21 had a T790M mutation-negative status, whereas 16 did not have T790M mutation assay when disease progression occurred.

Comparison of efficacy between two groups

Until December 2015, 270 patients (99.60%) achieved the end point of disease progression or death. PFS in the combination group (16.89 months, 95% confidence interval [CI]: 13.89–20.11) was significantly higher compared with the sequential group (9.90 months, $p < 0.001$; Figure 1a). PFS in the combination group was 16.89 months (95% CI: 13.89–20.11), which was significantly higher than PFS2 in the sequential group (14.05 months, 95% CI: 11.78–14.22, $p = 0.009$; Figure 1b). The OS of the patients was 33.22 months (95% CI: 26.99–37.01) in the combination group and 26.47 months (95% CI: 25.05–26.95) in the sequential group ($p < 0.001$; Figure 1c). Further, the short-term best curative effects of all the patients are summarized in Table S1. The ORR was 79.31% in the combination group and 52.11% in the sequential group, which showed a significant difference ($\chi^2 = 18.160$, $p < 0.001$).

Propensity score matching

To further explore the efficacy of icotinib combined with chemotherapy for patients, propensity score matching (PSM)

TABLE 1 Demographics and baseline disease characteristics of patients

	No. of patients	Treatment groups		p value
		Combination group	Sequential group	
All	271 (100%)	58 (21.40%)	213 (78.60%)	
Sex				0.126
Female	184 (67.90%)	37 (63.80%)	147 (69.00%)	
Male	87 (32.10%)	21 (36.20%)	66 (31.00%)	
Age, years				0.716
<65	178 (65.68%)	37 (63.80%)	140 (65.70%)	
≥65	93 (34.32%)	21 (36.20%)	73 (34.30%)	
Smoking				0.745
Yes	67 (24.70%)	14 (24.10%)	54 (25.40%)	
No	204 (75.30%)	44 (75.90%)	159 (74.60%)	
ECOG PS				0.856
0.1	243 (89.67%)	52 (89.66%)	191 (89.67%)	
≥2	28 (10.33%)	6 (10.34%)	22 (10.33%)	
Stage				0.078
IIIB	64 (23.62%)	15 (25.86%)	45 (21.13%)	
IV	207 (76.38%)	43 (74.14%)	168 (78.87%)	
EGFR mutation				0.440
19	139 (51.29%)	29 (50.00%)	110 (51.64%)	
21	132 (48.71%)	29 (50.00%)	103 (48.36%)	

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor.

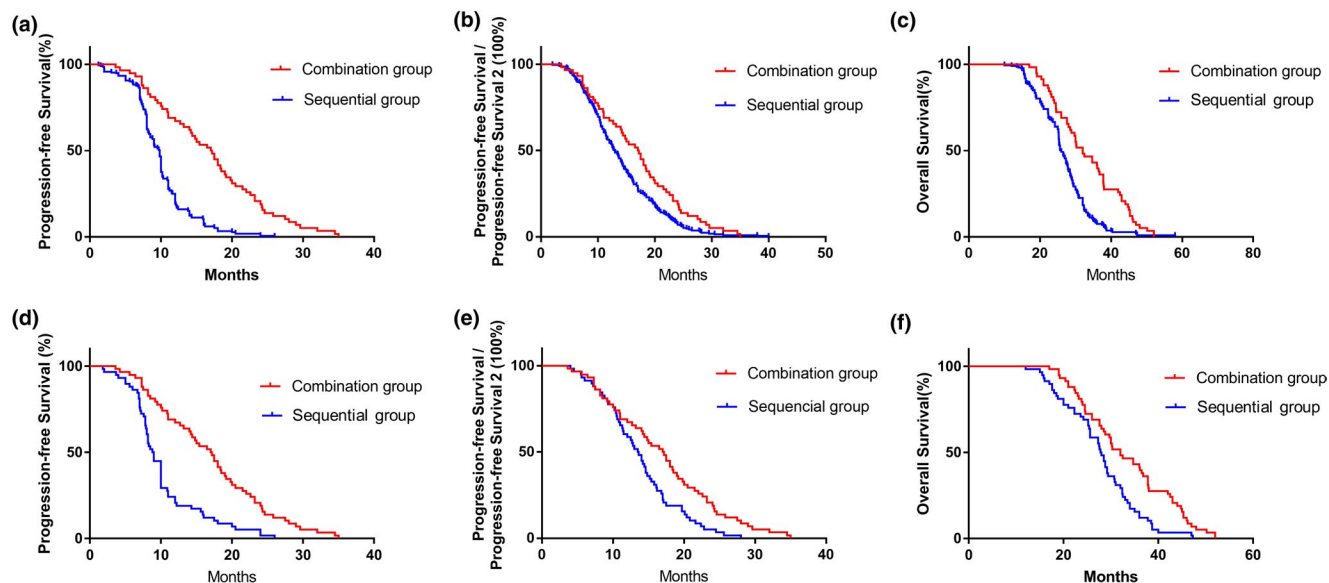


FIGURE 1 Kaplan–Meier (KM) plots. (a) KM plots of progression-free survival (PFS) comparing patients receiving different first-line treatment strategies. (b) KM plots of PFS in the combination group and PFS2 in the sequential group comparing patients receiving different treatment strategies. (c) KM plots of the overall survival (OS) comparing patients receiving different treatment strategies. (d) KM plots of PFS comparing patients receiving different treatment strategies in the propensity-matched cohort. (e) KM plots of PFS in the combination group and PFS2 in the sequential group comparing patients receiving different treatment strategies in the propensity-matched cohort. (f) KM plots of OS comparing patients receiving different treatment strategies in the propensity-matched cohort

was used to match the patients in the two groups according to the baseline characteristics of the patients—including, age, sex, ECOG, clinical tumor-node-metastasis staging (and the existence of brain metastasis), EGFR mutation status, and smoking. As a result, 58 pairs of matching patients were selected with balanced baseline disease characteristics. The PFS was 16.89 months in the combination group and 10.21 months in the sequential group ($p < 0.0001$; Figure 1d). The PFS for patients in the combination group (16.89 months) was also higher compared with the PFS2 in the sequential group (13.78 months, $p = 0.003$; Figure 1e). The OS for patients in the combination group and the sequential group were 33.22 and 27.71 months, respectively ($p = 0.001$; Figure 1f). The ORR in the combination group was better than that in the sequential group (79.31% vs. 51.72%; $\chi^2 = 12.093$, $p = 0.001$). The best overall responses of the patients based on RECIST are summarized in Table S2. The best responses of target lesions for 58 patients in PSM during the treatment are summarized in Figure 2.

Comparison of safety between two groups

The most common adverse events in the combination group (including rash, neutropenia, nausea, anemia, and thrombocytopenia) were slightly more than those in the sequential group. The most common adverse events of grades 3 and 4 were neutropenia (6 patients [10.34%] in the combination group and 19 patients [8.92%] in the sequential group), rash (6 patients

[10.34%] in the combination group and 6 patients [2.82%] in the sequential group), and leucopenia (5 patients [8.62%] in the combination group and 21 patients [9.86%] in the sequential group). Among the adverse events, we also observed that the aspartate aminotransferase/alanine aminotransferase elevation in the combination group (24 [41.38%]) was significantly higher than that in the sequential group (43 [20.19%]). The majority of the adverse events were grades 1 and 2, whereas the adverse events of grades 3 and 4 were rare. Moreover, there were no drug-related deaths (Table 2).

DISCUSSION

To explore the efficacy and safety of icotinib combined with pemetrexed plus platinum for untreated NSCLC with sensitive EGFR mutations, we retrospectively analyzed 271 patients who received the first-line icotinib combined with chemotherapy or received the first-line icotinib alone, followed by the second-line chemotherapy when the disease progressed. The PFS, PFS2, and OS in the combination group were significantly extended compared with the sequential group. Meanwhile, to balance the baseline characteristics of the patients and evenly distribute confounding factors in the two groups, we did PSM. The PFS, PFS2, and OS in the combination group were superior to those in the sequential group. These findings revealed that the first-line therapy of icotinib plus chemotherapy improved PFS and OS compared with the separate two-line therapy.

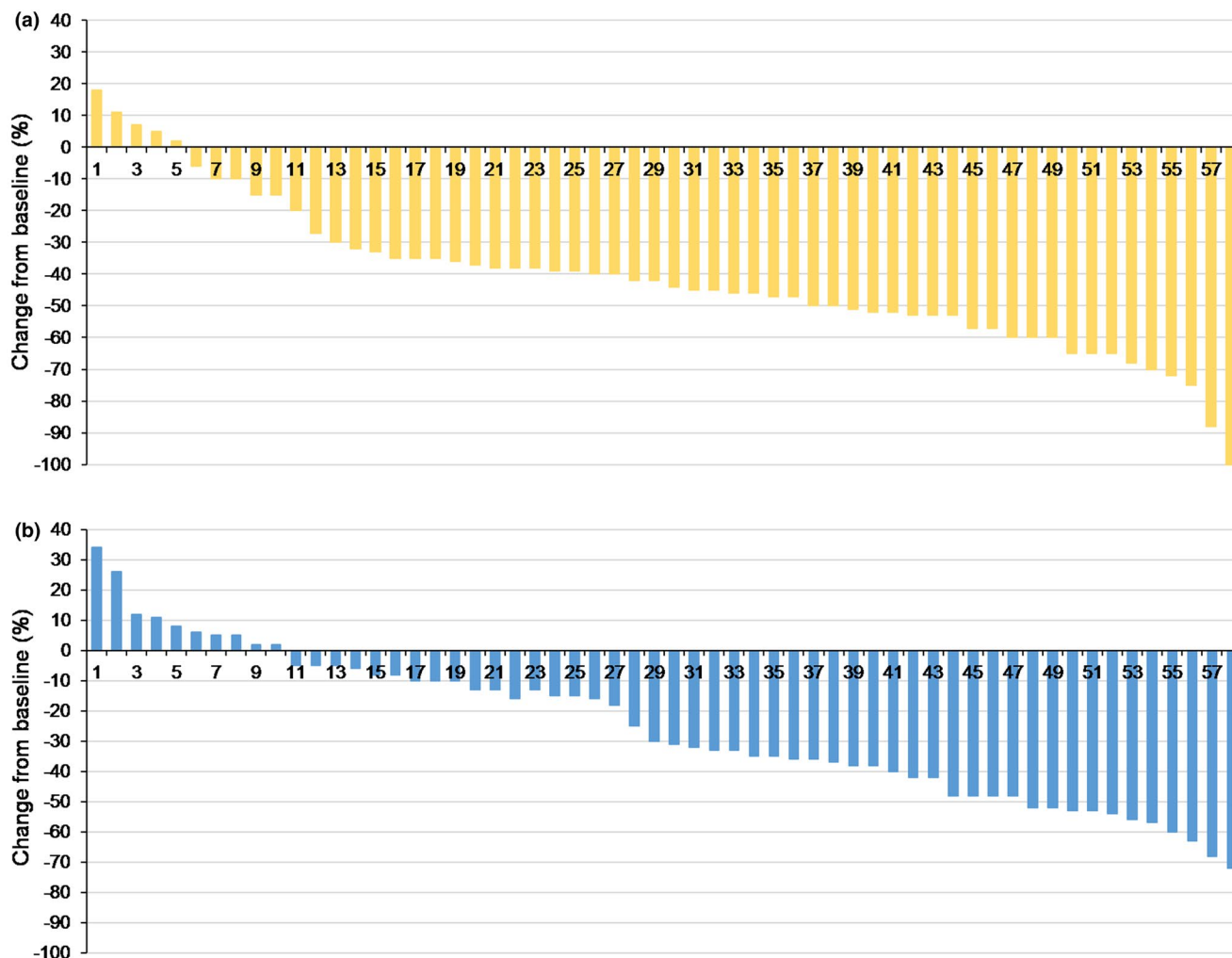


FIGURE 2 The best percent change in target lesions from baseline for 58 pairs of patients in the propensity-matched cohort. (a) The best responses of target lesions from baseline for the combination group. (b) The best responses of target lesions from baseline for the sequential group

It is well-known that somatic mutations of EGFR are associated with the sensitivity of lung cancer to EGFR-TKIs, and EGFR-TKIs are the standard first-line treatment for patients with advanced lung cancer with EGFR mutants. However, most patients develop acquired resistance after EGFR-TKIs treatment for about 10–14 months. EGFR T790M mutation is the most common mechanism of acquired EGFR-TKIs resistance and has been discovered in about 52–68% of patients with resistance to EGFR-TKIs.^{14,15} For patients with EGFR T790M mutation, osimertinib is significantly efficacious. However, patients without EGFR T790M mutation lack specific drugs, and chemotherapy is still the first choice.

In the past decades, platinum-based chemotherapy was still an important therapeutic strategy for many patients with lung cancer, despite limited survival benefits and several adverse events, such as bone marrow depression and vomiting. In the early stages, clinical researchers tried to combine EGFR-TKIs with chemotherapy. However, the combination strategy of EGFR-TKIs plus chemotherapy in most studies failed to improve survival compared with traditional chemotherapy.^{16,17}

These failures were mostly caused by the patients’ selection—patients with wild-type EGFR cannot benefit from the treatment of EGFR-TKIs. Subsequently, three Asian studies proved that EGFR-TKIs plus chemotherapy could provide superior survival than chemotherapy alone.^{18–20} Then a three-arm study demonstrated that chemotherapy combined with EGFR-TKIs provided superior survival benefits compared with chemotherapy alone or EGFR-TKIs alone for patients with EGFR mutants.¹⁰ The strategy of chemotherapy combined with EGFR-TKIs could be a new choice for patients with advanced and sensitive EGFR-mutant lung adenocarcinoma in the early stage of treatment.

There is heterogeneity in lung cancer, which means that there are some cells with EGFR-negative mutations in lung cancer and others with EGFR-positive mutations. Early use of EGFR-TKIs combined with chemotherapy could improve patients’ survival.²¹ It has been reported that gefitinib combined with pemetrexed could increase cell growth inhibition, promote cell death, inhibit epithelial-to-mesenchymal transition, and guard against T790M mutation-mediated gefitinib resistance *in vitro*.²² In addition, in patients harboring EGFR

	Combination group (n = 58)		Sequential group (n = 213)		p value
	All (%)	Grades 3–4 (%)	All (%)	Grades 3–4 (%)	
Rash	35 (60.34%)	6 (10.34%)	85 (39.90%)	6 (2.82%)	0.006
Neutropenia	30 (51.72%)	6 (10.34%)	86 (40.37%)	19 (8.92%)	0.121
Nausea	32 (55.17%)	1 (1.72%)	75 (35.21%)	2 (0.94%)	0.006
Anemia	25 (43.10%)	2 (3.45%)	62 (29.11%)	3 (1.41%)	0.043
Thrombocytopenia	23 (39.66%)	4 (6.90%)	55 (25.82%)	2 (1.9%)	0.040
Leucopenia	14 (24.14%)	5 (8.62%)	50 (23.47%)	21 (9.86%)	0.916
Diarrhea	11 (19.00%)	2 (3.45%)	21 (9.86%)	1 (0.47%)	0.057
Vomiting	21 (36.20%)	1 (1.72%)	42 (19.72%)	2 (0.87%)	0.008
AST/ALT elevation	24 (41.38%)	4 (6.90%)	43 (20.19%)	3 (0.14%)	0.001
Fatigue	22 (37.93%)	0 (0%)	56 (26.29%)	1 (0.47%)	0.083

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

TABLE 2 Treatment-related adverse events

mutations and disease progression, first-line gefitinib combined with chemotherapy was compared with placebo plus chemotherapy; the results of this IMPRESS study showed that chemotherapy plus first-line gefitinib after disease progression did not prolong PFS for patients who received second-line chemotherapy.²³ Taken together, we could conclude that the therapy strategy of chemotherapy plus EGFR-TKIs in the early stage could provide better survival efficacy.

Our retrospective study revealed that EGFR-TKIs plus chemotherapy could provide superior PFS to EGFR-TKI alone, which is consistent with previous studies.^{9,10} Our findings also indicated that icotinib combined with pemetrexed plus platinum as first-line treatment could improve PFS, PFS2, OS, and ORR of patients with sensitive EGFR mutants and advanced lung adenocarcinoma compared with the separate two-line therapy. In other words, the combination therapy achieved better results, which showed a high remission rate and a low residual tumor load, reduced the diversity of tumor cells, and lowered the rate at which tumor cells produced drug-resistant cells to delay the arrival of drug resistance. Even drug-resistant tumor loads were at a lower level, reducing the risk of death from progression and making patients more likely to receive follow-up treatment.

We also found that the occurrence of all grades of adverse events in the combination group was slightly higher than that in the sequential group. However, these adverse events were tolerable. The most common adverse events of grades 3 and 4 in the combination group were neutropenia, leucopenia, and rash. There was no significant difference in the occurrence of grades 3 and 4 neutropenia and leucopenia between the combination group and sequential group, suggesting that bone marrow depression might be associated with chemotherapy.

Notably, the aspartate aminotransferase/alanine aminotransferase elevation in the combination group was significantly more than that in the sequential group, suggesting that

the combination group had more obvious hepatotoxicity compared with the sequential group. Considering that this may be related to the overlapping hepatotoxicity of icotinib, pemetrexed, and platinum, the combined application aggravates the liver's metabolic burden. It is recommended to evaluate liver function carefully before using the combined treatment. Combined therapy can be used in patients with better liver function ratings, but should be used with caution in patients with poor liver function assessment.

There were several limitations to our study. First, this study was a single-center retrospective analysis. Second, the sample size of this study was relatively small. Third, some patients who developed acquired EGFR-TKI resistance did not receive repeated tumor biopsies. Finally, three main limitations exist for PSM. First, PSM usually requires a relatively large sample size to achieve high-quality matching. Second, it requires a large common value range, except the propensity score based on the control group; otherwise, more observations will be lost, resulting in the remaining samples not being representative. Third, PSM only controls the influence of measurable variables, which will bring invisible bias if there is still unmeasured variable selection. In the future, therapeutic decisions regarding the treatment of NSCLC should be based on a prospective, randomized study with a larger sample size to evaluate the effect of sequencing versus combining the therapies.

In conclusion, this retrospective study confirmed that first-line pemetrexed plus platinum combined with icotinib improved PFS, PFS2, and ORR compared with first-line icotinib and second-line pemetrexed plus platinum when the disease progressed. Although combinational strategy caused a little more treatment-related adverse events, patients could tolerate it.

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

Y.Z. and L.X.F. wrote the manuscript. L.X.F. designed the research. J.W., Z.Y., H.G., and L.X.F. performed the research. Y.Z. and L.W.Z. analyzed the data. L.W.Z. and L.X.F. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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