RESEARCH ARTICLE

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Sequential Administration of EGFR-TKI and Pemetrexed Achieved a Long Duration of Response in Advanced NSCLC Patients with EGFR-mutant Tumours

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Abstract

Objectives: The optimal combination of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and chemotherapy has helped to improve therapeutic effects in non-small-cell lung cancer (NSCLC). This study aimed to explore the progression free survival (PFS) of patients after sequential administration of TKI and pemetrexed chemotherapy. **Methods:** This study retrospectively screened treatment-naive advanced NSCLC patients harbouring EGFR mutations who were prescribed a TKI and salvaged with pemetrexed chemotherapy or vice versa. The total, initial and salvage PFS were collected. **Results:** The total PFS including both the initial and salvage PFS was 18.0 mon (95% CI: 14.1–21.9 mon), which was not influenced by the sequence of administration (TKI first: 18.0 mon, 95% CI: 15.8–20.2 mon, pemetrexed first: 16.1 mon, 95% CI: 9.1–23.1 mon, HR 0.92, P=0.748). A longer PFS was achieved for TKI over chemotherapy in both the initial (10.6 and 5.9 mon, HR 2.62, P=0.001) and salvage therapy (12.0 and 6.0 mon, HR 1.29, P=0.001). TKI remained effective either before (10.6 mon) or after (12.0 mon) chemotherapy (HR 0.96, P=0.853). The same trend was observed for chemotherapy (5.9 and 6.0 mon for initial and salvage therapy, respectively, HR 0.82, P=0.417). **Conclusions:** The sequential administration of TKI and pemetrexed chemotherapy achieved a long PFS and was a suitable treatment for advanced NSCLC.

Keywords: NSCLC- EGFR-TKI- sequential administration- pemetrexed- PFS

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Introduction

Background

Currently, lung cancer ranks No. 1 in both morbidity and mortality worldwide (Hirsch et al., 2009; Siegel et al., 2018). Non-small-cell lung cancer (NSCLC) constitutes approximately 80% of lung cancer cases. Most patients have a poor prognosis, and the 5-year survival is estimated to be only approximately 15%, despite the adoption of aggressive therapies (Torre et al., 2016). Progress in treating NSCLC was achieved recently. In non-squamous cancer, pemetrexed-based doublet chemotherapy achieved superior effects (Wu et al., 2014). In addition, studies have suggested treatments with epithelial growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) are more efficacious over chemotherapy in selected patients harbouring EGFR mutations (Paez et al., 2004; Zhou et al., 2015; Cheng et al., 2016; Mok et al., 2009). Efforts were devoted to combine these two efficacious therapies together (Lee et al., 2013; Yang et al., 2016). In the pilot JMIT study, the progression-free survival (PFS) of a combination of gefitinib and pemetrexed (15.8 months) was better than that of gefitinib alone (10.9 months). However, the possible benefits of pemetrexed were excluded in the gefitinib arm in this study, i.e., the effects of the sequential administration of TKI and pemetrexed were not seriously evaluated.

To explore the outcome of their sequential administration, a retrospective study was performed. We screened 1,682 consecutive NSCLC patients treated from 2012 to 2017 and selected 94 patients for the current analysis.

Materials and Methods

Study Population

This retrospective study was conducted on patients admitted to the West China Hospital from March 2012 to Jan 2017, and consecutive patients were screened against the inclusion criteria, namely, pathologically confirmed, metastatic (stage IV according to the 7th edition AJCC cancer staging manual), treatment-naive NSCLC patients harbouring sensitive EGFR mutations (exon 19 deletion, exon 21 L858R missense mutation, or others) were who were prescribed an EGFR TKI and salvaged by pemetrexed-based doublet chemotherapy upon tumour

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progression (Progressive Disease, PD) (Rice et al., 2010; Eisenhauer et al., 2009). In addition, patients who received these two treatments in a reverse sequence, i.e., pemetrexed doublet chemotherapy salvaged by EGFR TKI, were also included. Exclusion criteria were patients ≤18 years old, existing secondary malignancy, presence of primary resistance mutation (T790M), or complex small-cell lung cancer. Local palliative radiotherapy for bone or brain metastases was allowed. The ethical committee of Sichuan University reviewed the study concept and the study was performed in accordance with the Declaration of Helsinki.

Treatment Protocol

Pemetrexed (Lily, IL) was intravenously infused at a dose of 500 mg/m^2 on day 1 of each 21-day cycle, supplemented with folic acid, vitamin B12, and dexamethasone, as per the pemetrexed prescribing information. Gefitinib (250 mg, AstraZeneca, UK) and erlotinib (150 mg, Roche, Switzerland) were both taken orally once per day, and icotinib (125 mg, Beta, China) was taken 3 times a day. Treatment continued until disease progression, unacceptable toxicity, or another situation occurred for which it was considered inappropriate to continue.

Outcome Measures

Tumours were assessed regularly every 2 months radiographically, including computed tomography of the chest and upper abdomen, magnetic resonance imaging of the head, and bone scintigraphy. The tumour response was determined by the treating physicians. Tumour response was described as a complete response (CR), a partial response (PR), stable disease (SD), or progressive disease (PD) based on the RECIST 1.1. The total PFS (PFSt) was defined as the duration from the initiation of the therapy to the date of first onset of PD during the salvage therapy. PFSt included both the PFS of the initial therapy (either chemotherapy, PFS1c, or TKI, PFS1t) and the salvage therapy (chemotherapy, PFS2c, or TKI, PFS2t).

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM Inc., Chicago, IL) and the results of the multi-variate analysis were output by Stata MP 14 (Stata Corp LP., Chicago, IL). The quantitative data were compared using chi-square tests and Fischer's exact test according to Cochran's rule. Kaplan–Meier curves were used to compare survival. Multi-variate analysis was conducted by using a Cox proportional hazard model. All P-values were based on a two-tailed hypothesis, and statistical significance was assumed if $p < 0.05$.

Results

Patient characteristics

A cohort of consecutive 1,682 patients admitted during the time period was screened for inclusion. Those with an earlier stage (I–III) without a sensitive EGFR mutation, including unknown mutation status, treated with chemotherapy other than pemetrexed, or failure to accomplish both lines of therapies, were excluded. A total of 94 patients were thus enrolled in this study. Their demographic features are summarized in Table 1. The majority were women, non-smokers, had adenocarcinoma and were younger (<60).

Total PFS

The total PFS of the whole cohort, irrespective of administration sequence, was 18.0 mon (95% CI: 14.1–21.9 mon, Figure 1 A). Multivariate analysis indicated that subgroups including age, sex, smoking history, histology, PS score, and EGFR mutation type did not influence the PFS independently (Figure 2).

Therapeutic effects between variant administration sequence

Patients were grouped according to the sequence of chemotherapy and TKI. Those with initial chemotherapy (CT group) were comparable to those of the reverse sequence of therapy (initial TKI therapy, TC group) in

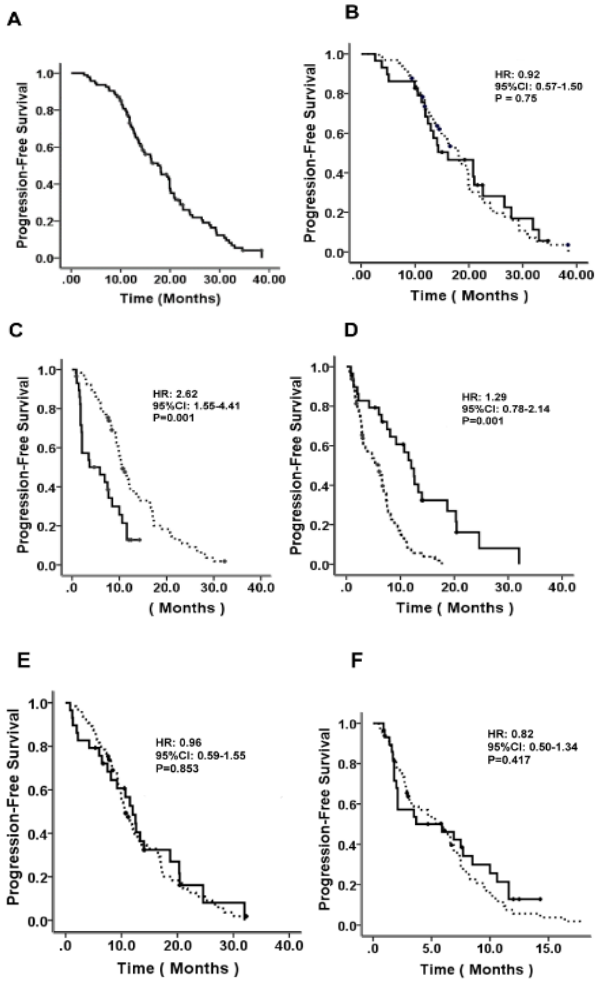

Figure 1. The Total PFS (PFSt) of the Whole Cohort (A), or CT (Solid Line) and TC (Dash Line) Group Respectively (B). Targeted therapy achieved a longer PFS over chemotherapy both in the initial therapy (C, solid line, chemotherapy, dash line, targeted therapy) and salvage therapy (D, solid line: targeted therapy, dash line, chemotherapy). PFS of targeted therapy was similar between the initial therapy (dash line) and salvage therapy (solid line, E). Also, PFS of chemotherapy was comparable in the initial (solid line) and salvage therapy (dash line, F).

Table 1. Demographic Features of the Enrolled Patients

N (%)	Total 94 (100)	TKI followed by chemotherapy 65 (69.1)	Chemotherapy followed by TKI 23 (30.9)	P value
Sex				
Female	52 (55.3)	33 (35.1)	19 (20.2)	
Male	42 (44.7)	32 (34.1)	10 (10.6)	0.71
Age				
≤60	60 (63.8)	41 (43.6)	19 (20.2)	
>60	34 (36.2)	24 (25.6)	10 (10.6)	0.97
Smoking				
Yes	35 (37.2)	25 (26.6)	10 (10.6)	
No	59 (62.8)	40 (42.6)	19 (20.2)	0.64
Performance				
0	48 (51.1)	34 (36.2)	14 (14.9)	
1	46 (48.9)	31 (33.0)	15 (15.9)	0.12
Histology				
ADC	90 (95.7)	62 (66.0)	28 (29.7)	
Non-ADC	4 (4.3)	3 (3.2)	1 (1.1)	0.84
EGFR mutation				
Exon 19 Del	40 (42.6)	24 (25.5)	16 (17.1)	
L858R	40 (42.6)	33 (35.1)	7(7.5)	
Other	14 (14.8)	8 (8.5)		0.73

Abbreviations, ADC; adenocarcinoma; Non-ADC, non-adenocarcinoma.

demographic features (Table 1).

No CR was observed. Chemotherapy achieved a similar disease control rate (DCR, CR and SD combined) in the initial and salvage therapy (69.0% and 76.9%). Similarly, the DCR of TKI was comparable in its upfront and late use (93.8% and 86.2%). The efficiency of TKI was consistently better than that of chemotherapy. Less PD was observed in both initial (6.2% and 31.0%) and salvage therapy (13.8% and 23.1%, Figure 3).

At the time of preparing this manuscript (Sept 2017), 81 patients (86.2%) had progressed after both TKI and chemotherapy. The PFSt was similar between the CT group (16.1 mon, 95% CI: 9.1–23.1 mon) and the TC group (18.0 mon, 95% CI: 15.8–20.2 mon, HR 0.92, 95% CI: 0.57–1.50, P=0.75, Figure 1 B). A longer PFS was achieved for TKI over chemotherapy both in the initial (10.6 and 5.9 mon, HR 2.62, 95% CI: 1.55–4.41 mon, P=0.001) and salvage therapy (12.0 and 6.0 mon, HR 1.29, 95% CI: 0.78–2.14, P=0.001, Figure 1 C and D). TKI remained effective either before (10.6 mon) or after (12.0 mon) chemotherapy (HR 0.96, 95% CI: 0.59–1.55, P=0.853). The same trend was observed for

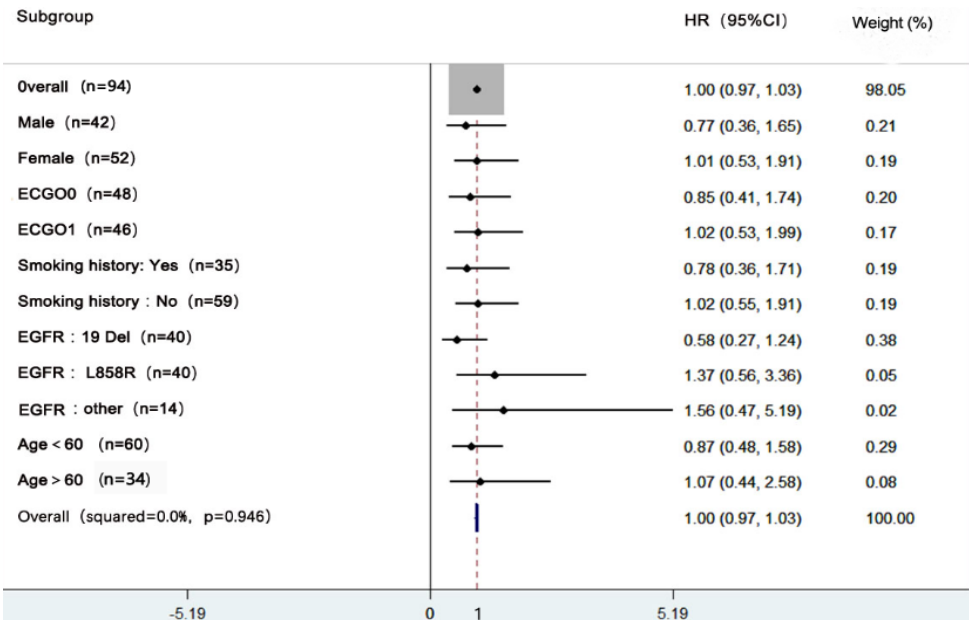

Figure 2. Subgroup Analysis of the PFSt

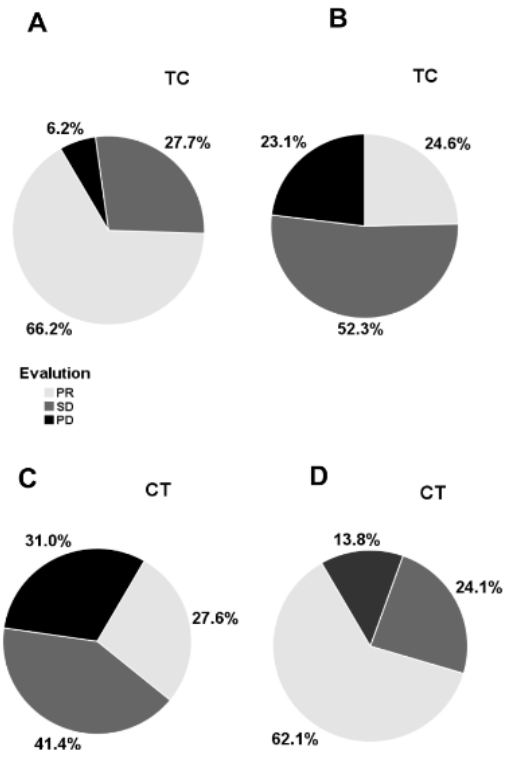

Figure 3. The Objective Responses of Chemotherapy or TKI in the TC (B and C) or CT Group (A and D) Therapy.

chemotherapy (5.9 and 6.0 mon for initial and salvage therapy, respectively, HR 0.82, 95% CI: 0.50–1.34, P=0.417, Figure 1 E and F). Most of our patients did not receive re-biopsy and the data on T790M resistance mutaion were lacking. Among 26 patients who had availabe T790M data, only 2 were found T790M(+) before chemotherapy. The low frequency of T790M(+) wouldn't impact much on our conclusion.

Discussion

In this retrospective study, consecutive 1,682 patients with NSCLC were screened against the inclusion criteria and 94 patients were enrolled in this study. This study found the sequential administration of TKI and pemetrexed doublet chemotherapy to the patients with tumours harbouring EGFR mutations achieved a long PFS (18.0 mon), irrespective of the order of the sequence. It was also found the PFS for either TKI or chemotherapy were similar in both the initial or salvage therapy. TKI consistently achieved a longer PFS over chemotherapy in both lines of therapy.

The combination of TKI and chemotherapy was once considered inappropriate. The pilot ISEL study where gefitinib was combined with chemotherapy showed the combination increased toxicity with no beneficial effects (Thatcher et al., 2005). However, the study recruited unselected patients with no regard to EGFR mutation status. Later, the FASTACT-2 study showed that intercalated chemotherapy and erlotinib prolonged PFS over chemotherapy, and the benefit was mostly restricted to the cohort with EGFR mutations (Wu et al., 2013). The JMIT study suggested that the combination of pemetrexed-based chemotherapy and gefitinib improved PFS compared with gefitinib monotherapy (15.8 and 10.9 mon) in patients with EGFR mutations. However, this study failed to provide information on the effects of pemetrexed and TKI administered sequentially. Any data about a direct comparison between concurrent and sequential use of TKI and pemetrexed chemotherapy were lacking. The total PFS of our study was similar to that of the JMIT study, which argues that the sequential administration of TKI and pemetrexed chemotherapy is also effective.

Given a comparable PFS, less toxicity would be expected in sequential compared with simultaneous administration of therapies. This hypothesis has been repeatedly confirmed in the FASTACT-2, JMIT, and other studies (Ahn et al., 2012). In addition, the failure of each therapy is easily recognizable and managed with ample reports in the sequential setting, which can be a challenge in simultaneous therapy. In certain situations, continuous TKI treatment beyond PD has been found to be beneficial (Tudor et al., 2017; Hsu et al., 2016). Lastly, the clinical schedule of each therapy was easily managed when they were used separately.

The long PFS achieved by the sequential administration has its underlying reasons. The PARAMOUNT study showed that first-line and maintenance pemetrexed doublet chemotherapy achieved a PFS of 7.9 mon (Paz-Ares et al., 2013). TKI treatment has a durable PFS (10.8–13.1 mon) in first line therapy, as reported by numerous studies (Maemondo et al., 2010; Fukuoka et al., 2011; Zhou et al., 2011; Sequist et al., 2013). TKI and pemetrexed chemotherapy both have good control of tumour growth without possible interference from the other. Second, a potential synergy between pemetrexed chemotherapy and TKI might exist (Giovannetti et al., 2008). Low thymidylate synthase expression is predictive of pemetrexed efficacy, and gefitinib suppresses its expression in NSCLC cell lines (Chamizo et al., 2015; Kim et al., 2009). In addition, one preclinical report showed an erlotinib-induced G1-phase arrest protected these cells from the cytotoxicity of subsequent exposure to pemetrexed. Cell cycle redistribution also supports sequential administration in order to avoid the possible antagonism between these therapies.

Whether initial chemotherapy treatment influences the following response to TKI or vice versa has not been thoroughly elucidated to date. In our study, TKI as initial or salvage therapy achieved a similar PFS (10.6 and 12.0 mon), which was consistent with a previous report (Zeng et al., 2014). However, in that article, chemotherapy in the initial therapy had a longer PFS, opposite to this study's findings. The reasons behind this difference remain elusive. However, in the current study, only pemetrexed (but not other chemotherapy agents) was included. Pemetrexed might achieve a longer PFS among other chemotherapy agents, regardless of its use as frontline or behind-line treatment (Scagliotti et al., 2008; Yang et al., 2016; Sun et al., 2012). Additionally, synergistic effects between pemetrexed chemotherapy and TKI have been reported previously. The findings of these reports may help to explain the difference.

The current study has its limitations. This was

a retrospective study conducted in a single institute. Selection bias is always inevitable in such studies and all of the conclusions require further confirmation. In addition, only PFS was included in this study, and data on survival were lacking because survival is often confounded by subsequent therapies. In addition, only patients with both TKI and pemetrexed chemotherapy were included in this study. Those without salvage therapy due to deleterious performance were excluded. This might lead to an overestimation of the treatment effects. These inclusion criteria were used because the aim of the study was to explore the effects of sequential administration of both therapies, and the cohort in this study was similar to that in the JMIT study.

In summary, the sequential administration of TKI and pemetrexed chemotherapy achieved a long duration of response in advanced NCLC patients with EGFR-mutant tumours, comparable to that of simultaneous administration reported in the JMIT study. The effects did not seem to be affected by the sequence of the therapy. The current study enrolled patients receiving both lines of therapies. Those not prescribed with any 2nd line therapy due to death or poor performance were excluded. This might contribute to the observed longer PFS over that in JMIT study. Our study argues for the sequential administration of TKI and pemetrexed chemotherapy would be an option in this population.

Acknowledgments

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