**Combination TS-1 plus EGFR-tyrosine kinase inhibitors (TKIs) for the treatment of non-small cell lung cancer after progression on first-line or further EGFR-TKIs: A phase II, single-arm trial**

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**Keywords**
Acquired resistance; EGFR-tyrosine kinase inhibitors; non-small cell lung cancer; phase II study; TS-1.

**Abstract**

**Background:** EGFR-tyrosine kinase inhibitors (TKIs) combined with TS-1 might overcome EGFR-TKI resistance, which has been indicated by several preclinical studies. We investigated the synergistic efficacy and safety of the combination therapy of EGFR-TKIs and TS-1 in non-small cell lung cancer (NSCLC) patients with acquired resistance to previous EGFR-TKI therapy.

**Methods:** This was a phase II, single-arm and single-center prospective study. Stage IIIB–IV NSCLC patients with acquired resistance to prior EGFR-TKI treatment were enrolled. All patients were administered combination therapy of TS-1 and continuing EGFR-TKIs in this study. The primary endpoints were progression-free survival (PFS), while overall survival (OS), disease control rate (DCR), and safety were secondary endpoints.

**Results:** A total of 42 patients with acquired resistance to EGFR-TKIs were eligible for this study. The median PFS for all patients was five months (95% confidence interval [CI] 3.6–5.4). The OS and DCR were 31.9 (95% CI 17.8–46.0) months and 69.0% (29/42), respectively. No grade 4 toxicity or grade 3 hematologic toxicity was observed in this study. One patient (2%) experienced grade 3 elevated total serum bilirubin.

**Conclusion:** The combination treatment of TS-1 and EGFR-TKIs was effective and well tolerated by patients who had experienced prior EGFR-TKI treatment failure. Our results need to be validated by larger prospective clinical trials.

**Introduction**

Lung cancer is the leading cause of cancer death worldwide¹,² and non-small cell lung cancer (NSCLC) accounts for 80–85% of cases. Studies have demonstrated that EGFR-tyrosine kinase inhibitor (TKI) therapy is strongly correlated with oncogenic mutations in the EGFR gene, such as exon 19 deletions and exon 21 mutations.³,⁴ Several phase III randomized trials concluded that metastatic patients with EGFR mutations administered EGFR-TKIs had increased PFS compared with those who received chemotherapy. However, EGFR-mutated NSCLC has an “Achilles heel.” All patients acquire resistance to EGFR-TKIs within a year;⁵,⁶ 50% of patients are T790M mutation positive, followed in second place by patients who acquire amplification of the wild type MET oncogene.⁷,⁸ In advanced NSCLC patients with acquired resistance, discontinuing TKIs can lead to accelerated cancer progression, which results from clonal heterogeneity in progression lesions. Several studies have suggested that continuing targeted treatment after acquired resistance may be beneficial.⁹–₁₂ The 2017 National Comprehensive Cancer Network (NCCN) guidelines recommend continuing TKI...
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Methods

Study design

This study was a phase II, open-label, single center and single-arm study. The Ethics Committee of the National Cancer Center and Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (Beijing, China) approved the study. Written, informed consent was obtained from all patients prior to enrollment. This study was conducted in accordance with the Good Clinical Practice Guidelines for Trials on Drugs and the Declaration of Helsinki.

Patients

All patients were enrolled from the same hospital from 2013 to 2016. Patients were pathologically confirmed with stage IIIB or IV advanced NSCLC and experienced failure of prior first-generation EGFR-TKI (gefitinib, erlotinib or icotinib) treatment. The participants of our study were previously treated with first-line or further monotherapy of first generation EGFR-TKIs (gefitinib, erlotinib or icotinib) for > 3 months, regardless of whether they developed EGFR exon 19 deletions or EGFR L858R mutations.

Acquired EGFR-TKI resistance in this study was defined as a prior radiographic response to EGFR-TKI therapy with later disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Study inclusion criteria were: age ≥ 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2 at the time of initial EGFR-TKI therapy, and a minimum life expectancy of 12 weeks. Exclusion criteria were: the existence of other tumors, EGFR-TKI or TS-1 intolerance, use of other drugs that influenced TS-1 efficacy, prior treatment including ≥ 2 EGFR-TKIs, and treatment with multiple targeted drugs.

Procedures

Patients received TS-1 adjusted by body surface area (BSA) as follows: < 1.25 m², 40 mg twice/day; ≥ 1.25 m² to < 1.5 m², 50 mg twice/day; and ≥ 1.5 m², 60 mg twice/day. This schedule was administered on days 1–14 every three weeks. All patients continually received the same subtype and dosage of EGFR-TKIs (150 mg erlotinib once a day; 250 mg gefitinib once a day; 125 mg icotinib three times a day). Tumor response was assessed every six weeks by computed tomography. Brain magnetic resonance imaging was also required for patients with known or suspected central nervous system metastases. Bone scanning was performed every year.

Outcomes

The primary endpoint was progression-free survival (PFS), which was defined as the duration from acquired resistance to objective tumor progression or the last follow up according to RECIST version 1.1. Secondary endpoints were overall survival (OS), disease control rate (DCR) and adverse events (AEs). OS was defined as the duration from acquired resistance to EGFR-TKIs to death or the last follow up. DCR was assessed by rate of patients with complete remission, partial remission, or stable disease. AEs were evaluated by laboratory examination, questionnaires, and clinical observation according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

The final follow-up was performed in September 2017 via hospital computer information systems, follow-up scans, and telephone calls. All information was uploaded into our database for analysis. Baseline data are presented as frequencies and percentages including age, gender, smoking history, PS, stage, histological subtype, EGFR mutation subtypes, EGFR-TKIs plus TS-1 line, EGFR-TKI subtypes, and the best efficacy after TKI treatment. The median and 95% confidence interval (CI) for PFS and OS were assessed using the Kaplan–Meier method. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY, USA).
Results

Patients’ clinical characteristics

A total of 42 NSCLC patients who met the inclusion criteria were enrolled in the study (Fig 1). The clinical characteristics of these patients are summarized in Table 1. There were similar proportions of subsets by gender, PS, EGFR mutation, and the best efficacy after EGFR therapy. Differences in baseline characteristics were recorded. The majority of patients in the study were aged < 65; 66.7% had no smoking history; 97.6% had stage IV lung cancer after initial EGFR-TKI treatment; and 92.9% were diagnosed with adenocarcinoma. Gefitinib was more commonly used than erlotinib and icotinib. Combination therapy of TS-1 and EGFR-TKIs was more often used as third-line or further treatment.

Primary efficacy

The median PFS for all patients was five months (95% CI 3.6–5.4) (Fig 2). The median OS was 31.9 months (95% CI 17.8–46.0) (Fig 3). The DCR was 69.0% (29/42) and no patients achieved a partial or complete response.

Safety

The most common toxicities were hematological and gastrointestinal (Table 2). No grade 4 toxicity or grade 3 hematologic toxicity occurred. One patient experienced grade 3 elevated total serum bilirubin.

Discussion

This study was designed to investigate the synergistic efficacy of the combined treatment of EGFR-TKIs and TS-1 for advanced NSCLC patients experiencing disease progression after EGFR-TKI treatment. Although the synergistic interaction of TS-1 and EGFR-TKIs has been confirmed,19,20 few studies have reported the efficacy in clinical scenarios. Herein, we suggest that combination

Table 1 Patient characteristics

| Characteristic                  | No. | %   |
|--------------------------------|-----|-----|
| Age, years                     |     |     |
| < 65                           | 33  | 78.6|
| ≥ 65                           | 9   | 21.4|
| Gender                         |     |     |
| Male                           | 21  | 50.0|
| Female                         | 21  | 50.0|
| Smoking history                |     |     |
| Absence                        | 28  | 66.7|
| Presence                       | 8   | 19.0|
| Unknown                        | 6   | 14.3|
| ECOG PS                        |     |     |
| 1                              | 19  | 45.2|
| 0                              | 23  | 54.8|
| Stage†                         |     |     |
| IIIB                           | 1   | 2.4 |
| IV                             | 41  | 97.6|
| Histological subtype           |     |     |
| Adenosquamous carcinoma        | 1   | 2.4 |
| Adenocarcinoma                 | 39  | 92.9|
| Unknown                        | 2   | 4.7 |
| Subtype of EGFR mutations      |     |     |
| Del19‡                         | 14  | 33.3|
| L858R§                         | 15  | 35.7|
| Unknown                        | 13  | 31.0|
| EGFR-TKI line                  |     |     |
| First-line                     | 10  | 24.3|
| First Maintenance¶             | 7   | 16.2|
| Second-line or further         | 25  | 59.5|
| EGFR-TKI subtype†              |     |     |
| Gefitinib                      | 27  | 64.2|
| Erlotinib                      | 8   | 19.0|
| Icotinib                       | 7   | 16.8|
| Best efficacy after TKIs       |     |     |
| PR                             | 19  | 45.2|
| SD                             | 23  | 54.8|

†American Joint Committee on Cancer 7th Edition Staging Manual. §Exon 19 deletions. ¶Exon 21point mutation. ¶¶Maintenance therapy after first-line therapy. ††The EGFR-tyrosine kinase inhibitor (TKI) subtype is the same with combination therapy of EGFR-TKIs and S-1 after patients acquired EGFR-TKI resistance. ECOG, Eastern Cooperative Oncology Group; PR, partial response; PS, performance status; SD, stable disease.
therapy was feasible, with a median PFS of five months, a median OS of 31.9 months, and a DCR of 69.0%. Furthermore, this treatment was well tolerated in the majority of patients, with only one patient experiencing grade 3 elevated total serum bilirubin without any clinical symptoms.

In 2017, the NCCN recommended osimertinib for T790M positive NSCLC patients with EGFR mutations who acquired resistance. Osimertinib, a third-generation TKI, is an inhibitor that selectively targets EGFR-sensitizing mutations and T790M. A multicenter, single-arm phase II clinical trial of 127 advanced NSCLC patients with acquired resistance to EGFR-TKI treatment reported that osimertinib could achieve a tumor response rate of 61% (95% CI 52–70) and a median PFS of 9.6 months (95% CI 8.3–not reached).21 The AURA2 trial also proved that osimertinib was beneficial for metastatic NSCLC patients with progression after EGFR-TKI treatment. The results showed that osimertinib was associated with a median PFS of 9.9 months (95% CI 8.5–12.3), and an objective responsive rate of 70% (95% CI 64–77).22 Osimertinib has indeed shown good clinical efficacy and manageable side effects in selected patients with EGFR T790M positive NSCLC, but in the real world there are many difficulties associated with the use of osimertinib, such as cost-effectiveness, specimen accessibility, and limited technology. In our study, the combination therapy of TS-1 plus EGFR-TKIs was applied to unselected patients, regardless of the existence of T790M mutations. The patients achieved PFS of five months; however, the median PFS of TS-1 and EGFR-TKIs was not comparable to osimertinib.

The 2017 NCCN panel recommended continuing erlotinib, gefitinib, or afatinib and/or local therapy for T790M negative patients with asymptomatic progression. Advanced NSCLC patients with EGFR mutations in the ASPIRATION study were treated with erlotinib, and decisions whether to extend erlotinib therapy after radiological progression were made by patients and/or physicians. The first median PFS (time to RECIST response or death) was 11.0 months (95% CI 9.2–11.1), and the second median PFS (duration from initiation to disease progression when erlotinib therapy was discontinued) was 14.1 months (95% CI 12.2–15.9).23 A phase II trial conducted to assess the

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**Table 2** Adverse events in patients administered S-1 and TKI combination therapy

| Adverse events                          | Grade III | Grade II | Grade I | Normal |
|----------------------------------------|-----------|----------|---------|--------|
| Hematological system                   |           |          |         |        |
| Leucopenia                             | 0         | 1        | 8       | 33     |
| Neutropenia                            | 0         | 3        | 5       | 34     |
| Anemia                                 | 0         | 1        | 4       | 37     |
| Thrombocytopenia                       | 0         | 0        | 0       | 42     |
| Liver Function                         |           |          |         |        |
| AST                                     | 0         | 0        | 10      | 32     |
| ALT                                     | 0         | 0        | 9       | 33     |
| Total Bilirubin                        | 1         | 7        | 9       | 25     |
| Renal function                         |           |          |         |        |
| Cr                                      | 0         | 0        | 2       | 40     |
| Systemic manifestations                |           |          |         |        |
| Fatigue                                | 0         | 0        | 2       | 40     |
| Pyrexia                                | 0         | 0        | 0       | 42     |
| Mucocutaneous                          |           |          |         |        |
| Rash                                   | 0         | 3        | 2       | 37     |
| Dermatitis acniform                    | 0         | 0        | 0       | 42     |
| Pigmentation                           | 0         | 2        | 5       | 35     |
| Pruritus                               | 0         | 0        | 1       | 41     |
| Stomatitis                             | 0         | 2        | 3       | 37     |
| Alimentary system                      |           |          |         |        |
| Nausea                                 | 0         | 3        | 7       | 32     |
| Vomiting                               | 0         | 3        | 2       | 37     |
| Diarrhea                               | 0         | 4        | 2       | 36     |
| Abdominal pain                         | 0         | 1        | 0       | 41     |

TKI, tyrosine kinase inhibitor.
efficacy of continual gefitinib administration in Italian patients who experienced prior EGFR-TKI treatment failure reported a median PFS of 2.8 months (95% CI 2.4–3.1), and median OS of 10.2 months (95% CI 8.8–14.1).24 Our result showed better clinical efficacy with PFS of five months compared to these previous prospective studies. Goto et al. recently reported that patients with progressive disease who continued gefitinib treatment achieved PFS of five months. However, their definition of progressive disease depended on the judgment of the attending physician, not RECIST as used in our study. In addition, the median OS of 31.9 months observed in our study was much longer than their result of 15.3 months OS.25

Because the efficacy of continuous EGFR-TKI monotherapy is relatively moderate, many studies have evaluated the efficacy of EGFR-TKIs combined with other agents, such as chemotherapy, antiangiogenic drugs, or monoclonal antibodies. In the real world, many patients receive pemetrexed plus platinum chemotherapy and achieve PFS of 4.9–5.4 months and OS of 16.1–19.5 months after they develop symptomatic resistance to EGFR-TKI treatment.26,27 The IMPRESS study showed that continuing gefitinib and chemotherapy (cisplatin plus pemetrexed) did not prolong the median PFS (5.4 months in both groups) and was also detrimental to the median OS (13.4 vs. 19.5 months, HR 1.44, 95% CI 1.07–1.94; \( P = 0.16 \)) compared to the placebo plus chemotherapy. Nearly 5% of patients in the IMPRESS study experienced grade 3 or worse AEs, including anemia and neutropenia.27,28 In regard to antiangiogenic drugs, two studies retrospectively evaluated combination treatment of EGFR-TKIs and bevacizumab. One study observed severe toxic effects, such as rash, paronychia, hypertension, and anemia, while the other found hypertension (44%), fatigue (37%), and hand-foot syndromes (18.5%); median PFS was 4.1 and 5.33 months, respectively.29,30 A trial of cetuximab and afatinib reported that the PFS (4.6 vs. 4.8 months; \( P = 0.643 \)) was not significantly different between patients with and without T790M mutations and the grade 3/4 AE rate was 44/2 %.31 We observed better tolerance and a lower grade 3/4 AE rate in our study compared to previous studies of combination therapy. Considering the advantage of oral medication and lower toxicity, this combination therapy of continuous EGFR-TKIs and TS-1 was acceptable. The median PFS of five months in our study was also comparable to prior data.

There were some limitations to our study. Because T790M was not regularly detected at the Chinese Academy of Medical Sciences until 2017, T790M was not mandatorily detected in our study. We also did not define different subgroups, such as asymptomatic or symptomatic disease progression, as the relevant data was not available in our database. As a single-arm prospective study, the difference between combination therapy and EGFR-TKI monotherapy was not investigated, although the benefit of combination therapy of TS-1 with continuing EGFR-TKIs was remarkable compared to the results of previous monotherapy studies.

To sum up, our results demonstrate that combination therapy of TS-1 and EGFR-TKIs could be a beneficial, well-tolerated, and cost-effective option for patients once they acquire resistance to EGFR-TKIs. MET amplification is a primary mechanism of resistance to AZD9291, which targets T790M mutation.32 Whether this combined treatment could be an option for patients with acquired resistance to AZD9291 is an interesting question.

This study was an exploratory trial, suggesting that combined treatment of TS-1 and EGFR-TKIs is helpful and applicable in Asian NSCLC patients who acquire resistance to EGFR-TKI treatment. However, these conclusions need to be confirmed by larger clinical studies.

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Disclosure

No authors report any conflict of interest.

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