ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 June 26; 10(18): 5934-6340

Published by Baishideng Publishing Group Inc

WJCC

World Journal of Clinical Cases

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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

PUBLICATION DATE

June 26, 2022

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2022 June 26; 10(18): 6069-6081

DOI: 10.12998/wjcc.v10.i18.6069

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Randomized Controlled Trial

Sequential chemotherapy and icotinib as first-line treatment for advanced epidermal growth factor receptor-mutated non-small cell lung cancer

Sheng-Jie Sun, Jin-Di Han, Wei Liu, Zhi-Yong Wu, Xiao Zhao, Xiang Yan, Shun-Chang Jiao, Jian Fang

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Chiu CC, Taiwan; Roudi R, United States; Singh I, United States

Received: November 22, 2021
Peer-review started: November 22, 2021
First decision: February 7, 2022
Revised: March 13, 2022
Accepted: April 15, 2022
Article in press: April 15, 2022
Published online: June 26, 2022

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Abstract

BACKGROUND

Icotinib could have potential effect and tolerability when used sequentially with chemotherapy for advanced epidermal growth factor receptor (*EGFR*)-mutated non-small cell lung cancer (NSCLC).

AIM

To evaluate the efficacy and safety of chemotherapy followed by icotinib maintenance therapy as first-line treatment for advanced *EGFR*-mutated NSCLC.

METHODS

This multicenter, open-label, pilot randomized controlled trial enrolled 68 *EGFR*-mutated stage IIIB/IV NSCLC patients randomized 2:3 to the icotinib alone and chemotherapy + icotinib groups.

RESULTS

The median progression-free survival in the icotinib alone and chemotherapy + icotinib groups was 8.0 mo (95%CI: 3.84-11.63) and 13.4 mo (95%CI: 10.18-16.33), respectively (P = 0.0249). No significant differences were found in the curative

effect when considering different cycles of chemotherapy or chemotherapy regimen (all $P > 0.05$).

CONCLUSION

A sequential combination of chemotherapy and EGFR-tyrosine kinase inhibitor is feasible for stage IV *EGFR*-mutated NSCLC patients.

Key Words: Advanced stage; Chemotherapy; Epidermal growth factor receptor mutation; First-line treatment; Icotinib

Core Tip: The combination of chemotherapy and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) (concomitant or intercalated) generally showed improved efficacy compared with EGFR-TKI alone as the first-line treatment for advanced non-small cell lung cancer (NSCLC). This study aimed to evaluate the efficacy and safety of chemotherapy followed by icotinib maintenance therapy as first-line treatment for advanced *EGFR*-mutated NSCLC. Sixty-eight advanced NSCLC patients were randomized 2:3 to icotinib-alone or chemotherapy plus icotinib. The chemotherapy plus icotinib group showed higher progression-free survival than the icotinib alone group. Our study suggested that the sequential combination of chemotherapy and EGFR-tyrosine kinase inhibitor is feasible for stage IV *EGFR*-mutated NSCLC patients.

Citation: Sun SJ, Han JD, Liu W, Wu ZY, Zhao X, Yan X, Jiao SC, Fang J. Sequential chemotherapy and icotinib as first-line treatment for advanced epidermal growth factor receptor-mutated non-small cell lung cancer. *World J Clin Cases* 2022; 10(18): 6069-6081

URL: https://www.wjgnet.com/2307-8960/full/v10/i18/6069.htm

DOI: https://dx.doi.org/10.12998/wjcc.v10.i18.6069

INTRODUCTION

Globally, lung cancer is the malignancy with the highest incidence and mortality. In 2018, 2.1 million new lung cancers and 1.8 million deaths were reported, with an annual age-standardized incidence rate of 22.5 per 100000 individuals and an age-standardized yearly mortality rate of 18.6 per 100000 individuals[1]. Non-small cell lung cancers (NSCLCs) represent the greatest number (85%-90%) of malignant lung tumors[2], and almost half of NSCLCs are adenocarcinomas. Adenocarcinomas display activating mutations in the epithelial growth factor receptor (*EGFR*) gene, making such cancers candidates for EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy[3-5]. In Asians, individuals harboring *EGFR* mutations account for 51.4% of adenocarcinoma NSCLCs[3-5]. Currently, EGFR-TKIs are the guideline-recommended first-line treatment for advanced NSCLC with *EGFR* mutations[5].

Despite the improvement in progression-free survival (PFS) by EGFR-TKIs, acquired resistance inevitably develops after about 10 mo of treatment[3,6]. Due to the complexity of the EGFR-TKI resistance mechanisms[6-8], a combined treatment approach could be used to prevent or delay resistance development[7]. One of the combination therapies of interest and most frequently explored is chemotherapy + TKI. In clinical trials, a combination of chemotherapy and EGFR-TKI (concomitant or intercalated) generally showed improved efficacy compared with EGFR-TKI alone as the first-line treatment for advanced NSCLC[9-13]. Nevertheless, the best combinational strategy remains controversial.

In preclinical studies, compared with concurrent administration of gefitinib alone, the sequential administration of pemetrexed or paclitaxel with gefitinib exerted stronger anti-tumor activity by enhancing cell cytotoxicity[14-18]. Sequential chemotherapy followed by maintenance EGFR-TKI therapy may be a potential strategy, as suggested by recent clinical trials[19-21]. Icotinib was suggested to have potential effects and tolerability when used sequentially with chemotherapy[22-24]. Therefore, the present pilot study aimed to evaluate the efficacy and safety of different sequential combinations of chemotherapy (varying cycle number and chemotherapeutic agents), followed by icotinib maintenance *vs* icotinib alone as a first-line treatment for advanced *EGFR*-mutated NSCLC. The results might help improve the treatment strategies for these patients.

MATERIALS AND METHODS

Study design and patients

This multicenter, open-label, pilot randomized controlled trial (RCT) was conducted in four centers in China between November 2012 and July 2015. The study was carried out according to the principles of the Declaration of Helsinki and the guidelines of the Good Clinical Practice of the International Council for Harmonization. The trial was approved by the ethics committees of General Hospital of People's Liberation Army. All patients signed an informed consent form before any study procedure.

The inclusion criteria were: (1) Age 18-72 years; (2) patients with treatment-naïve advanced lung cancer having *EGFR*-sensitive mutation confirmed by pathological examinations; (3) stage IIIB or IV lung cancer; (4) Eastern Cooperative Oncology Group (ECOG) score of 0-2; (5) normal cardiac, liver, and renal functions, and routine blood test results; (6) expected survival > 3 mo; (7) negative urine pregnancy test within 7 d before screening for women of child-bearing age, and agreement to apply effective contraception measures to prevent pregnancy during and within 3 mo after the study for fertile men and women; and (8) signed informed consent forms. The exclusion criteria were: (1) Brain metastases; (2) active infection (according to the judgment of investigators); (3) major organ failure, such as decompensated cardiopulmonary failure; (4) newly developed myocardial infarction or cerebral infarction within 3 mo; (5) presence of a second malignant tumor (except for cured cervical cancer or skin cancer); (6) interstitial lung disease; or (7) pregnant or breastfeeding women.

Trial registration: ClinicalTrials.gov, NCT01665417. Registered on August 12, 2012, https://clinicaltrials.gov/ct2/show/NCT01665417.

Randomization and blinding

This study involved three randomizations. The patients were first randomized 2:3 to icotinib-alone *vs* chemotherapy + icotinib. The patients in the chemotherapy group were then randomized 1:1 to two *vs* four cycles of chemotherapy and further randomized 1:1 to pemetrexed and cisplatin (PP) *vs* docetaxel and cisplatin (DP) (Figure 1). All randomizations were carried out using a central randomization system designed by an independent biostatistician. The stratification factors after randomization included clinical stage (IIIB *vs* IV), type of *EGFR* mutation (exon 19 mutation *vs* exon 21 mutation), ECOG score (0-1 *vs* 2), and smoking status (non-smokers *vs* mild smokers *vs* regular smokers). This study was a pilot study, and the patients, treating physicians, and data assessors could not be blind to treatment allocation due to the nature of the treatments.

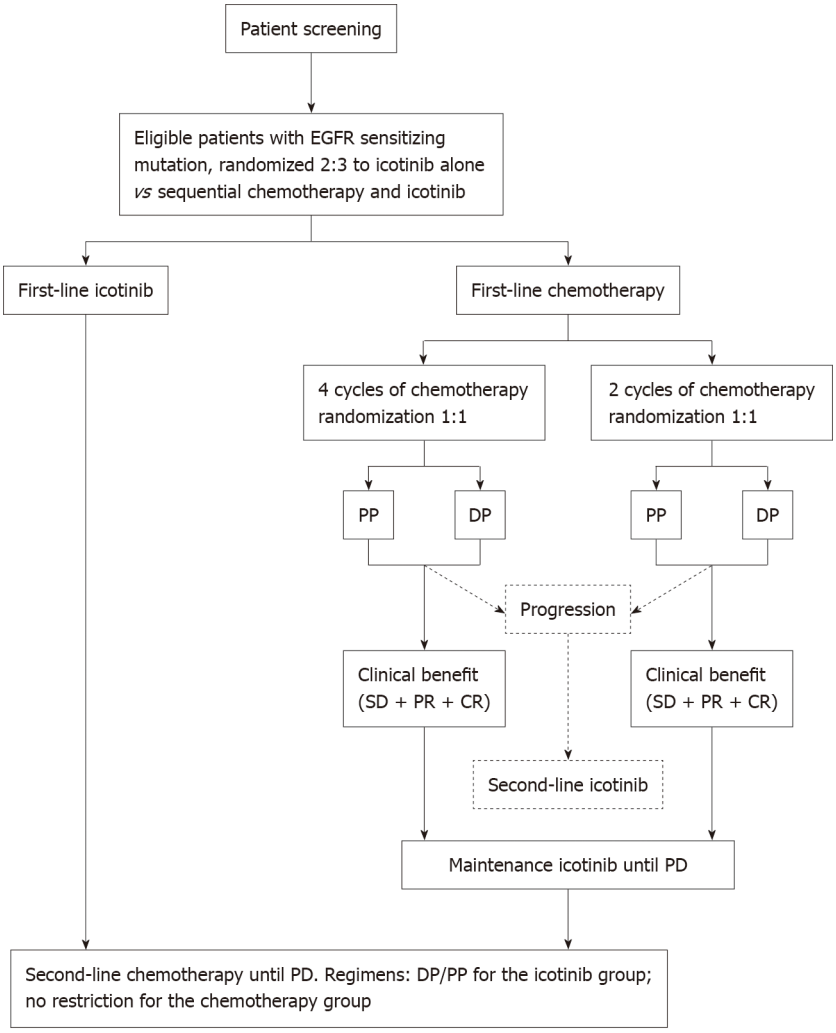
Treatment

Icotinib was provided by Betta Pharmaceutical Co., Ltd. (Zhejiang, China). Two or four cycles of PP (pemetrexed disodium 500 mg/m^2 iv d1, cisplatin 75 mg/m^2 iv d1, q3w) or DP (docetaxel 75 mg/m^2 iv d1, cisplatin 75 mg/m^2 iv d1, q3w) were administered to the patients assigned to the first-line chemotherapy + icotinib treatment. Icotinib hydrochloride (oral, 125 mg, tid) was used as maintenance therapy or second-line therapy until disease progression or the occurrence of severe toxicity for patients with clinical benefits or progressive disease after chemotherapy. Second-line chemotherapy after disease progression on icotinib was the crossover of the first-line chemotherapy. The chemotherapy regimen after DP/PP treatment had no restriction.

For the patients assigned to first-line icotinib treatment, 125 mg icotinib was administered orally three times per day until disease progression or the occurrence of severe toxicity. For second-line treatment, the patients received the PP (pemetrexed disodium 500 mg/m^2 iv d1, cisplatin 75 mg/m^2 iv d1, q3w) or DP (docetaxel 75 mg/m^2 iv d1, cisplatin 75 mg/m^2 iv d1, q3w) chemotherapy regimen, at the discretion of the treating physician.

Assessment

For patients on first-line chemotherapy, the tumor response was assessed after every two cycles of chemotherapy. During icotinib maintenance therapy, treatment efficacy assessment was performed 4 wk after treatment initiation and then every 6 wk until disease progression. For patients on first-line icotinib therapy, tumor response was assessed 4 wk after treatment initiation and then every 6 wk until disease progression. The tumors were assessed by plain and enhanced pulmonary computed tomography (CT) scanning, abdominal ultrasound examination, CT scanning or magnetic resonance imaging (MRI), ultrasound examination of superficial lymph nodes, brain MRI (if necessary), and emission CT (if necessary). The response to treatment was classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to RECIST 1.1[25]. The safety evaluation was performed using physical examinations and laboratory examinations (hematological and blood biochemical examinations). All adverse events were recorded from the informed consent until 30 d after the last dose of the study drug. The severity of the adverse events was assessed and documented according to the National Cancer Institute-Common Toxicity Criteria 3.0. The investigators judged the relationship between the adverse events and treatment.



DOI: 10.12998/wjcc.v10.i18.6069

Figure 1 Study design. DP: Docetaxel/cisplatin; EGFR: Epithelial growth factor receptor; PD: Progressive disease; PP: Pemetrexed/cisplatin; PR: Partial response; SD: Stable disease.

Outcomes

The study's primary endpoint was PFS, defined as the date of the start of treatment to the date of PD (per RECIST 1.1) or death, whichever occurred first. The secondary endpoint was overall survival (OS), defined as the time from the start of treatment to death. Other efficacy endpoints included overall response rate (ORR) and disease control rate (DCR). The ORR was defined as the proportion of patients achieving CR or PR, and the DCR was defined as the proportion of patients achieving CR, PR, or SD.

Statistical analysis

All analyses were performed using SAS 9.2 (SAS Institute, Inc., NC, United States). The efficacy analysis was performed in the full analysis set, defined as all randomized patients who received at least one dose of the study drug. The safety set included all randomized patients who received at least one dose of the study drug. Continuous data are presented as means ± SD and medians (ranges). Categorical data are presented as numbers (percentages). PFS and OS were analyzed using the Kaplan-Meier method and the log-rank test. The ORR and DCR were summarized as percentages and Clopper-Pearson 95%CIs. Two-sided P values of < 0.05 were considered statistically significant.

RESULTS

Characteristics of the participants

Between November 2012 and July 2015, 68 participants were recruited: 24 in the icotinib-alone group and 44 in the chemotherapy + icotinib group. The participants who received single-dose treatment (22 in the icotinib-alone group and 36 in the chemotherapy + icotinib group) were included in the analysis. All participants were randomized, and treatment was initiated. The characteristics of the participants are

shown in Table 1. All patients except one had stage IV NSCLC.

Response to treatment

Table 2 shows the responses to treatment. No participants achieved CR. In the icotinib-alone group, the ORR was 54.5% (95%CI: 32.2-75.6) and the DCR was 90.9% (95%CI: 70.8-98.9) compared with 44.1% (95%CI: 27.2-62.1) and 97.1% (95%CI: 84.7-99.9), respectively, in the chemotherapy + icotinib group.

When considering the number of chemotherapy cycles, the ORR was 47.6% (95%CI: 25.7-70.2) and the DCR was 100.0% (95%CI: 83.9-100.0) for two cycles, and the ORR was 38.5% (95%CI: 13.9-68.4) and the DCR was 92.3% (95%CI: 64.0-99.8) for four cycles. When considering the chemotherapy types, the ORR was 40.0% (95%CI: 16.3-67.7) and the DCR was 100.0% (95%CI: 78.2-100.0) for DP, and the ORR was 47.4% (95%CI: 24.4-71.1) and the DCR was 94.7% (95%CI: 74.0-99.9) for PP. When considering each chemotherapy regimen, the ORR was 33.3%-60.0%, and the DCR was 88.9%-100%.

Survival

In the icotinib group, the median follow-up was 23.1 (range, 2.5-71.9) mo. The median follow-up in the chemotherapy + icotinib group was 36.0 (range, 5.1-75.7) mo. Figures 2 and 3 present the PFS and OS, respectively. The median PFS in the icotinib-alone and chemotherapy + icotinib groups was 8.0 mo (95%CI: 3.8-11.6) *vs* 13.4 mo (95%CI: 10.2-16.3), respectively (P = 0.0249). The median OS was 23.1 (95%CI: 9.7-50.3) *vs* 36.0 mo (95%CI: 22.2-45.4), respectively (P = 0.4511). The median PFS of the participants who received two and four chemotherapy cycles was 12.1 mo *vs* 15.1 mo, and the median OS was 36.1 mo *vs* 33.9 mo, with no significant differences (PFS, P = 0.6605; OS, P = 0.9239). The PFS after two cycles of DP, two cycles of PP, four cycles of DP, and four cycles of PP was 11.9, 15.2, 15.2, and 15.1 mo, respectively; the median OS was 36.1, 28.0, 36.1, and 33.9 mo, respectively. No significant difference was observed among the different treatment regimens (PFS, P = 0.1815; OS, P = 0.9549).

Table 3 presents the treatment received after icotinib-based therapy. The treatment profile was similar in the two groups.

Treatment-related adverse events

The rates of all-grade treatment-related adverse events (TRAEs) were lower in the icotinib-alone group compared with the chemotherapy + icotinib group, and included rash (40.9% *vs* 55.9%), gastrointestinal system disorders (0.0% *vs* 82.4%), alanine transaminase elevation (27.3% *vs* 41.2%), aspartate aminotransferase elevation (13.6% *vs* 29.4%), leukopenia (0.0% *vs* 64.7%), and thrombocytopenia (0.0% *vs* 11.8%). Grade 3-4 TRAEs were not observed in the icotinib-alone group. However, grade 3-4 gastrointestinal system disorders (5.9%) and leukopenia (8.8%) were recorded in the chemotherapy + icotinib group (Table 4).

DISCUSSION

Sequential chemotherapy followed by maintenance TKI may be a potential strategy for advanced NSCLC with *EGFR* mutation. However, the optimal regimen remains to be determined. In this study, icotinib was selected because of the potential effect and tolerability of sequential chemotherapy and icotinib[22-24]. The present study indicated that the sequential combination of chemotherapy followed by icotinib improved PFS by 5.4 mo compared with icotinib alone as the first-line therapy of NSCLC. In addition, no differences were observed between two and four cycles of chemotherapy and between PP and DP. Therefore, for patients with advanced NSCLC with *EGFR* mutation, a sequential combination of chemotherapy and an EGFR-TKI is feasible. Considering the chemotherapy toxicity, the efficacy of a two-cycle chemotherapy regimen was comparable to that of a four-cycle chemotherapy regimen.

In the present study, no significant differences were observed in OS (36 mo *vs* 23.1 mo) and PFS (8.0 mo *vs* 13.4 mo), which was probably due to the small sample size or the fact of crossover of the treatment group upon disease progression. Considering the synergistic effect of EGFR-TKIs and chemotherapy in the elimination of tumor cells, as reported by some preclinical studies, gefitinib and erlotinib were combined with two chemotherapy regimens (cisplatin + gemcitabine; carboplatin + paclitaxel), thus launching four large phase III clinical studies, including INTACT 1 and 2 and TRIBUTE [26,27]. These studies showed no significant difference between chemotherapy and combined treatment groups (PFS and OS), which might be because the participants were not selected according to their *EGFR* mutation status[28]. A retrospective analysis of the OPTIMAL study on *EGFR* mutation (exon 19 deletion or exon 21 L858R mutation) showed that the OS of patients treated with chemotherapy alone was significantly lower than that of patients who received TKI and sequential chemotherapy [median OS: 11.2 *vs* 29.7 mo, HR = 2.97 (1.74-5.07)]. Although it was a retrospective analysis, it also suggested that sequential treatment with TKI and chemotherapy for selected patients with *EGFR* mutation could prolong patient OS[29]. However, a phase II clinical study in Japan, NEJ00, reported that in NSCLC patients with *EGFR* mutation, the combined therapy of gefitinib, pemetrexed, and carboplatin was significantly superior to chemotherapy followed by targeted therapy[30]. Among the 80 enrolled patients, 41 received concurrent combination therapy, while 39 also had sequential therapy. The median

Table 1 Patient characteristics

	Icotinib	Chemotherapy + icotinib	Chemotherapy + icotinib, *n* = 34			
			2DP	2PP	4DP	4PP
	n = 22	*n* = 34	*n* = 11	*n* = 10	*n* = 4	*n* = 9
Age (yr)	57.0 ± 7.4	52.7 ± 11.05	52.9 ± 11.5	49.8 ± 9.2	49.8 ± 13.7	57.1 ± 11.7
Sex						
Male	11 (50.0)	9 (26.5)	2 (18.2)	2 (20.0)	2 (50.0)	3 (33.3)
Female	11 (50.0)	25 (73.5)	9 (81.8)	8 (80.0)	2 (50.0)	6 (66.7)
Stage						
IIIB	0	1 (2.9)	0	0	0	1 (11.1)
IV	22 (100.0)	33 (97.1)	11 (100.0)	10 (100.0)	4 (100.0)	8 (88.9)
EGFR mutation						
19 Del	12 (54.5)	19 (55.9)	5 (45.5)	5 (50.0)	4 (100.0)	5 (55.6)
21 L858R	7 (31.8)	14 (41.2)	5 (45.5)	5 (50.0)	0	4 (44.4)
Other	3 (13.6)	1 (2.9)	1 (9.1)	0	0	0
Smoking						
Yes	6 (27.3)	4 (11.8)	1 (9.1)	1 (10.0)	1 (25.0)	1 (11.1)
No	15 (68.2)	30 (88.2)	10 (90.9)	9 (90.0)	3 (75.0)	8 (88.9)
Quit smoking	1 (4.5)	0	0	0	0	0
ECOG PS						
0	5 (22.7)	6 (17.6)	1 (9.1)	2 (20.0)	0	3 (33.3)
1	13 (59.1)	25 (73.5)	7 (63.6)	8 (80.0)	4 (100.0)	6 (66.7)
2	2 (9.1)	0	0	0	0	0
Other	2 (9.1)	3 (8.8)	3 (27.3)	0	0	0

Data are mean ± SD or number (%). *EGFR*: Epithelial growth factor receptor; ECOG PS: Eastern Cooperative Oncology Group performance status.

PFS was 18.3 mo *vs* 15.3 mo [HR = 0.71 (0.42-1.2), P = 0.02], and median OS was 41.9 mo *vs* 30.7 mo [HR = 0.51 (0.26-0.99), P = 0.042], respectively. The response rates in the two groups were similar (87.8% and 84.6%, respectively). Furthermore, phase II clinical studies conducted in China reported similar results for gefitinib combined with pemetrexed-based chemotherapy[31]. Based on the results of NEJ005, the phase III clinical study NEJ009 further confirmed that the efficacy of gefitinib combined with carboplatin and pemetrexed was superior to that of single-drug gefitinib treatment[32], which showed that the PFS was 20.9 mo (18.0-24.2) *vs* 11.2 mo (9.0-13.4) [HR = 0.43 (0.39-0.62), P < 0.001], and more importantly, OS was 52.2 mo *vs* 38.8 mo (HR = 0.69, P = 0.013). Subsequently, CTRI/2016/08/007149, conducted in India and almost completely similar to NEJ009, further confirmed that the efficacy of gefitinib combined with carboplatin and pemetrexed was significantly superior to that of gefitinib alone [33]. It also demonstrated that the PFS of gefitinib combined with pemetrexed-based chemotherapy was longer than 16 mo and longer than 20.9 mo in NEJ009, which was a much longer PFS than achieved by gefitinib alone. In particular, two phase III clinical trials, NEJ009 and CTRI/2016/08/007149, confirmed the benefits of OS in the combination treatment group. The studies mentioned above mainly focused on targeting, a synchronous combination of chemotherapy, or alternating sequential combination of targeting and chemotherapy. However, evidence on the use of sequential therapy based on chemotherapy followed by the target drug in *EGFR*-mutant patients is lacking. Studies at the molecular level confirmed that sequential chemotherapy with the EGFR-TKI erlotinib after docetaxel could enhance the M-phase stagnation of tumor cell division and growth, resulting in cell apoptosis. They suggested a synergistic effect between molecular targeted therapy and appropriate sequential chemotherapy. These experimental results indicated that the use of chemotherapy first to induce tumor cell stagnation and apoptosis in the M phase, followed by EGFR-TKIs to enhance this effect[34], would result in sequential therapy having a superposition effect, which might be used as a feasible option. Similar to the present study, Han *et al*[13] compared gefitinib + pemetrexed + carboplatin *vs* gefitinib alone *vs* pemetrexed + carboplatin and reported a higher ORR with the TKI + chemotherapy

Table 2 Response to treatment

	n	PR (95%CI)	SD (95%CI)	PD (95%CI)	NE (95%CI)	ORR (95%CI)	DCR (95%CI)
Icotinib	22	54.5 (32.2-75.6)	36.4 (17.2-59.3)	4.5 (0.1-22.8)	4.5 (0.1-22.8)	54.5 (32.2-75.6)	90.9 (70.8-98.9)
Chemotherapy + icotinib	34	44.1 (27.2-62.1)	52.9 (35.1-70.2)	2.9 (0.1-15.3)		44.1 (27.2-62.1)	97.1 (84.7-99.9)
2-cycle chemo	21	47.6 (25.7-70.2)	52.4 (29.8-74.3)			47.6 (25.7-70.2)	100.0 (83.9-100.0)
2DP	11	36.4 (10.9-69.2)	63.6 (30.8-89.1)			36.4 (10.9-69.2)	100.0 (71.5-100.0)
2PP	10	60.0 (26.2-87.8)	40.0 (12.2-73.8)			60.0 (26.2-87.8)	100.0 (69.2-100.0)
4-cycle chemo	13	38.5 (13.9-68.4)	53.8 (25.1-80.8)	7.7 (0.2-36.0)		38.5 (13.9-68.4)	92.3 (64.0-99.8)
4DP	4	50.0 (6.8-93.2)	50.0 (6.8-93.2)			50.0 (6.8-93.2)	100.0 (39.8-100.0)
4PP	9	33.3 (7.5-70.1)	55.6 (21.2-86.3)	11.1 (0.3-48.2)		33.3 (7.5-70.1)	88.9 (51.8-99.7)
DP	15	40.0 (16.3-67.7)	60.0 (32.3-83.7)			40.0 (16.3-67.7)	100.0 (78.2- 100.0)
PP	19	47.4 (24.4-71.1)	47.4 (24.4-71.1)	5.3 (0.1-26.0)		47.4 (24.4-71.1)	94.7 (74.0-99.9)
Total	56	48.2 (34.7-62.0)	46.4 (33.0-60.3)	3.6 (0.4-12.3)	1.8 (0.0-9.6)	48.2 (34.7-62.0)	94.6 (85.1-98.9)

DCR: Disease control rate; NE: Not evaluable; ORR: Overall response rate; PD: Progressive disease; PR: Partial response; SD: Stable disease.

Table 3 Subsequent treatments

	Icotinib	Chemotherapy + icotinib	Chemotherapy + icotinib, *n* = 34			
			2DP	2PP	4DP	4PP
	n = 22	*n* = 34	*n* = 11	*n* = 10	*n* = 4	*n* = 9
Chemotherapy	13 (59.1)	16 (47.1)	6 (54.6)	4 (40.0)	2 (50.0)	4 (44.4)
Osimertinib	10 (45.5)	17 (50.0)	6 (54.6)	4 (40.0)	2 (50.0)	5 (55.6)
Other TKI	2 (9.1)	3 (8.8)	1 (9.1)	0	0	2 (22.2)
Radiotherapy	3 (13.6)	7 (20.6)	1 (9.1)	3 (30.0)	2 (50.0)	2 (22.2)
Other	3 (13.6)	5 (14.7)	1 (9.1)	2 (20.0)	0	2 (22.2)

TKI: Tyrosine kinase inhibitor.

Table 4 Possible treatment-related adverse events

	All-grade TRAE		Grade 3-4 TRAE	
	Icotinib (*n* = 22)	Chemotherapy + icotinib (*n* = 34)	Icotinib (*n* = 22)	Chemotherapy + icotinib (*n* = 34)
Rash	9 (40.9)	19 (55.9)	0 (0.0)	0 (0.0)
Gastrointestinal system disorders	0 (0.0)	28 (82.4)	0 (0.0)	2 (5.9)
Alanine transaminase elevation	6 (27.3)	14 (41.2)	0 (0.0)	0 (0.0)
Aspartate aminotransferase elevation	3 (13.6)	10 (29.4)	0 (0.0)	0 (0.0)
Leukopenia	0 (0.0)	22 (64.7)	0 (0.0)	3 (8.8)
Thrombocytopenia	0 (0.0)	4 (11.8)	0 (0.0)	0 (0.0)

TRAE: Treatment-related adverse event.

combination than for TKI alone or chemotherapy alone (82.5% *vs* 65.9% *vs* 32.5%), with similar trends in PFS and OS. Similar results were also reported by Wen *et al*[35] and Yan *et al*[36]. Another RCT focused on first-line chemotherapy and TKI sequential treatment in patients with advanced non-squamous NSCLC[37,38]. PFS and OS were similar in the pemetrexed + cisplatin + gefitinib and gefitinib monotherapy groups in the ITT population and *EGFR*-mutated subgroup, but the sample size in the

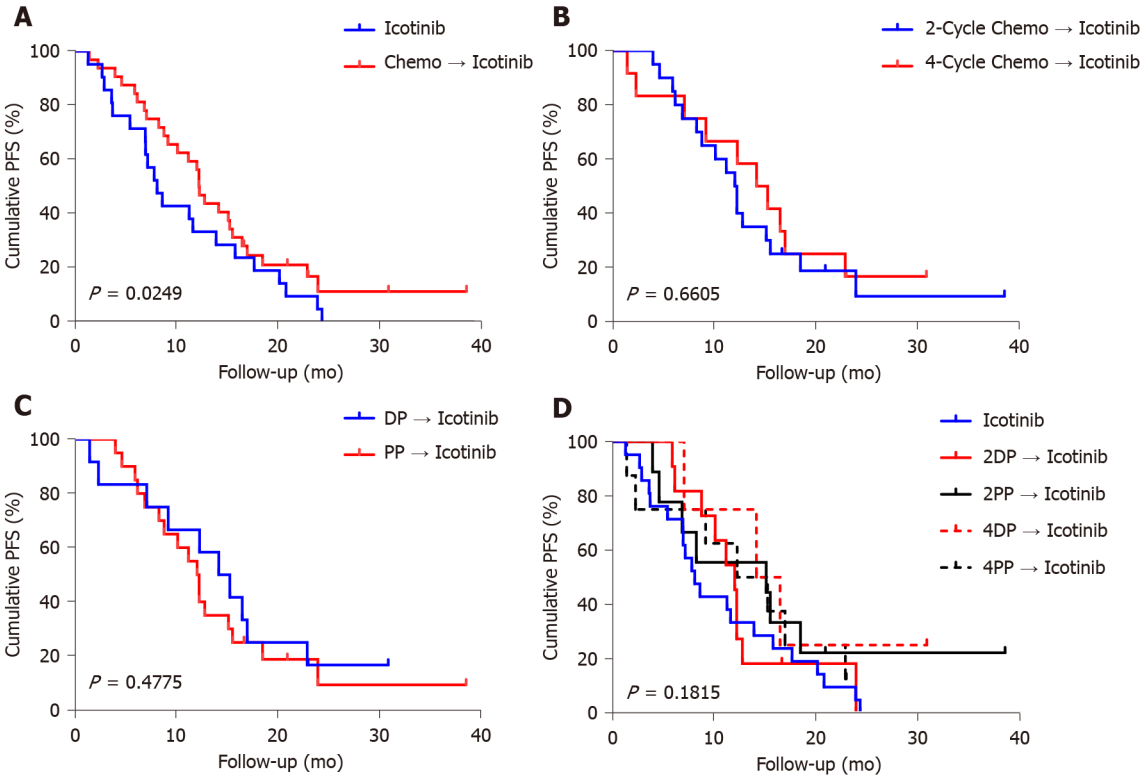


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Figure 2 Progression-free survival of patients. A: Progression-free survival (PFS) with icotinib *vs* chemotherapy followed by icotinib; B: PFS with two-cycle chemotherapy followed by icotinib *vs* four-cycle chemotherapy followed by icotinib; C: PFS with DP followed by icotinib *vs* PP followed by icotinib; D: PFS with icotinib *vs* various chemotherapy regimens followed by icotinib. DP: Docetaxel/cisplatin; PP: Pemetrexed/cisplatin.

EGFR-mutated subgroup was too small to draw a firm conclusion. The combination therapy may outperform the monotherapy ORR as chemotherapy and TKIs do not affect the cancer cells using the same mechanisms (*i.e.*, hitting the cells in multiple ways), and intratumor heterogeneity may be present (*i.e.*, using multiple drugs increases the likelihood of killing cells resistant to one of the drugs used). The immune system can also be activated[9,34,39,40]. Nevertheless, the PFS in the sequential treatment group in the present study was superior to that in the TKI-alone therapy group. The reason for the inconsistent results in these two studies might be that the number of patients with *EGFR* mutation in either study was small, affecting the consistency of the study results. Of note, the recent results of the FLAURA trial showed that first-line osimertinib achieved better OS and PFS than the comparator EGFR-TKIs[41], and sequential osimertinib with chemotherapy as a first-line option should be investigated. Due to the TRAE profile of osimertinib, the sequential use of chemotherapy and osimertinib could decrease the occurrence of TRAEs in the first-line treatment of NSCLC. Furthermore, the combination of EGFR-TKIs with vascular endothelial growth factor inhibitors could be a potential strategic option[42] and should also be examined.

In the present study, four cycles of chemotherapy were not better in terms of ORR, DCR, PFS, and OS compared with two cycles. Two cycles might be enough to eliminate tumor cells sensitive to chemotherapy and activate the immune system, while four cycles might lead to adverse events and decreases in blood immune cells[43]. In addition, fewer cycles could help reduce the physical, psychological, and economic burden of chemotherapy[43]. The rate of grade ≥ 3 TRAEs was 14.3% in the two-cycle subgroup and 15.4% in the four-cycle subgroup. Hence, the present study suggests similar efficacy and safety for the two- and four-cycle regimens, which could be supported by a meta-analysis that suggested no added benefit of six cycles of first-line chemotherapy compared with three and four cycles [43]. However, this study was not powered to compare two- *vs* four-cycle regimens, and additional studies are necessary to examine this point.

There are many therapeutic options in lung cancer, including chemotherapy, targeted therapy, and immunotherapy[2,44-48]. Icotinib is a promising targeted therapy for *EGFR*-mutated NSCLC[18,22-24]. The present study selected the combination of icotinib (or other EGFR-TKIs) and chemotherapy since it is the most studied combination in NSCLC, with apparent benefits in response and survival[9,18,24,34-36,49]. Still, the combination of EGFR-TKIs and immunotherapy could be a promising option for NSCLC[50-52], but some evidence suggests that immunotherapy is not effective in patients with *EGFR*-mutated NSCLC, probably because of the specific tumor microenvironment[52,53]. Indeed, early trials showed that immunotherapy monotherapy was inferior to EGFR-TKIs in *EGFR*-mutated NSCLC[52,

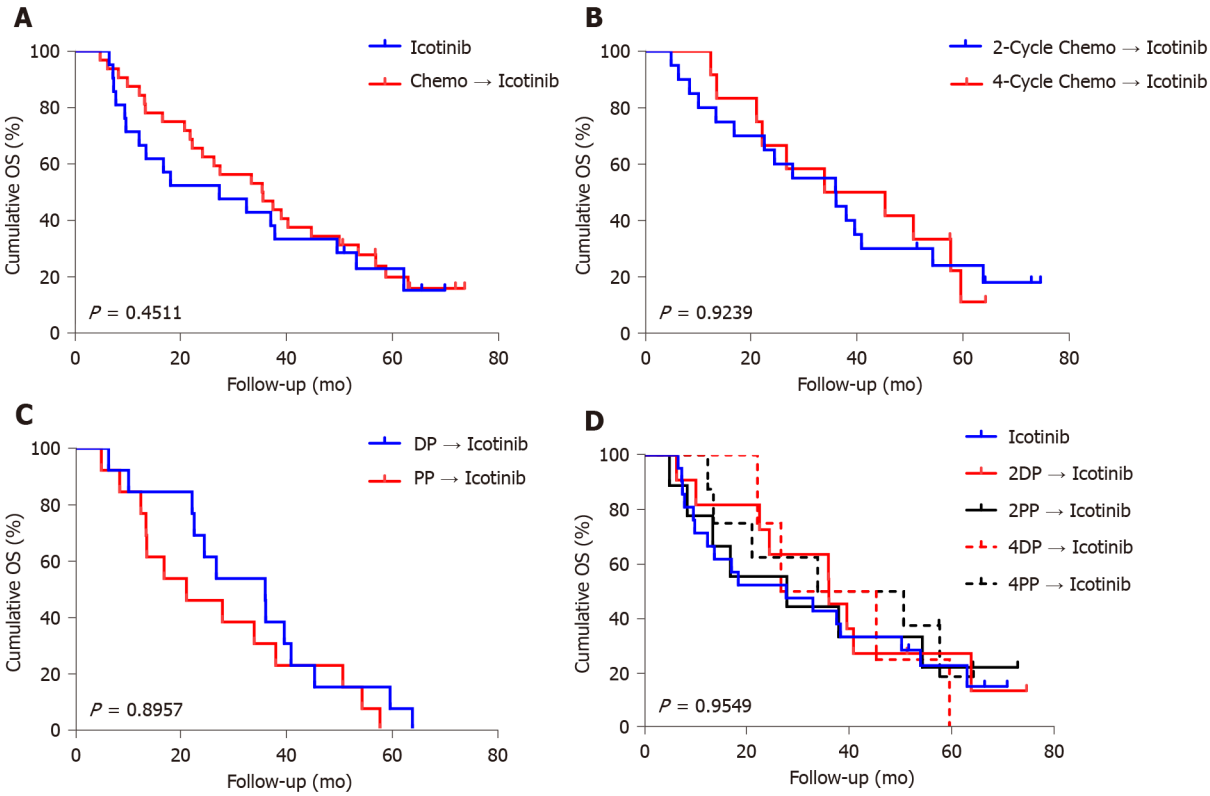

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Figure 3 Overall survival of patients. A: Overall survival (OS) with icotinib *vs* chemotherapy followed by icotinib; B: OS with two-cycle chemotherapy followed by icotinib *vs* four-cycle chemotherapy followed by icotinib; C: OS with docetaxel/cisplatin followed by icotinib *vs* PP followed by icotinib; D: OS with icotinib *vs* various chemotherapy regimens followed by icotinib. DP: Docetaxel/cisplatin; PP: Pemetrexed/cisplatin.

53]. Subsequent studies showed that the combination of immunotherapy with EGFR-TKIs in *EGFR*-mutated NSCLC resulted in high rates of serious AEs (33.3%-71.4% of grade 3-4 AEs)[54-56]. Therefore, additional studies are necessary before being able to use immunotherapy with EGFR-TKIs in patients with *EGFR*-mutated NSCLC.

Roviello *et al*[57] reported that EGFR-TKIs led to good outcomes in older adults with *EGFR*-mutated NSCLC. We agree that EGFR-TKIs could be a valuable and less toxic treatment option for older adults who often have difficulties with chemotherapy. Unfortunately, in the present study, the sample size was too small to be able to examine the influence of age on the treatment outcomes. Furthermore, as per the inclusion criteria, no patients > 72 years old were enrolled. Nevertheless, examining treatment options specifically in older adults is indeed a future direction for research.

This study had some limitations. This study was an exploratory study with a small sample size, and the analysis of OS had limited power. In addition, it was restricted to Chinese patients. It was an investigator-initiated trial. Only icotinib was provided, and the patients had to pay for the chemotherapy. This could have influenced recruitment. Although the trial was open to stage IIIB-IV patients, only one stage IIIB participant was actually recruited, mostly limiting the conclusions to stage IV patients. Due to the limited generalizability, the efficacy of sequential chemotherapy followed by TKI in the Caucasian population requires further investigation. Whether the results could also be generalized to non-stage IV patients remains to be examined.

CONCLUSION

For patients with stage IV NSCLC and *EGFR* mutation, sequential chemotherapy followed by TKI maintenance therapy is feasible. No significant differences were found in terms of the influence of the different number of chemotherapy cycles or different chemotherapy drugs on the curative effect, suggesting that fewer chemotherapy cycles could result in the same therapeutic effect in these specific patients.

ARTICLE HIGHLIGHTS

Research background

In 2018, 2.1 million new lung cancers and 1.8 million deaths were reported, and non-small cell lung cancers (NSCLCs) represent the greatest number (85%-90%) of malignant lung tumors. In Asians, 51.4% of epidermal growth factor receptor (*EGFR*)-mutated NSCLC was reported and EGFR-tyrosine kinase inhibitors (TKIs) have proved to be an effective treatment for this population.

Research motivation

Drug resistance always occurs after 10 mo of EGFR-TKIs treatment, and combination therapy could be an alternative to solve this difficulty. However, the most adequate combinational strategy remains controversial.

Research objectives

Some clinical studies have reported that sequential chemotherapy followed by maintenance EGFR-TKIs might be a potential strategy compared with EGFR-TKIs monotherapy. The efficacy and tolerability of icotinib has been demonstrated in many studies. Therefore, this pilot randomized controlled trial (RCT) aims to evaluate the efficacy and safety of combination therapy compared with monotherapy.

Research methods

This multicenter, open-label, pilot RCT enrolled 68 *EGFR*-mutated stage IIIB/IV NSCLC patients randomized 2:3 to the icotinib-alone and chemotherapy + icotinib groups.

Research results

A statistically significant difference was observed between the icotinib-alone and chemotherapy + icotinib groups regarding median progression-free survival (P = 0.0249). No statistically significant difference was found between two and four cycles of chemotherapy which means that the sequential combination of chemotherapy and EGFR-TKIs is feasible. Sequential chemotherapy followed by maintenance EGFR-TKIs might be a potential strategy for *EGFR*-mutated NSCLC patients; however, the optimal regimen remains to be determined.

Research conclusions

The sequential combination of chemotherapy and EGFR-TKIs could be a feasible strategy for stage IV *EGFR*-mutated NSCLC patients. It is suggested that 2-cycle sequential combination chemotherapy could have similar effectiveness to that of 4-cycle sequential combination chemotherapy in these patients.

Research perspectives

Future studies should involve a large population from multiple centers around the world to further validate the efficacy and safety of sequential treatment in *EGFR*-mutated NSCLC patients.

FOOTNOTES

Author contributions: Sun SJ, Jiao SC, and Fang J carried out the studies, participated in collecting data, and drafted the manuscript; Han JD and Liu W performed the statistical analysis and participated in its design; Wu ZY, Zhao X, and Yan X participated in the acquisition, analysis, interpretation of data and drafted the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by General Hospital of People's Liberation Army.

Clinical trial registration statement: ClinicalTrials.gov, NCT01665417. Registered on August 12, 2012, https://clinicaltrials.gov/ct2/show/NCT01665417.

Informed consent statement: All patients signed an informed consent form before any study procedure.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: The raw dataset analyzed in the current study are available from the corresponding author on reasonable request.

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S-Editor: Zhang H
L-Editor: Webster JR
P-Editor: Zhang H

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