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WORD COUNT 4017
TIME SUBMITTED 07-APR-2022 04:28PM
PAPER ID 84554577

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 73337

Manuscript Type: 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

Sun SJ *et al*. Chemotherapy plus icotinib for advanced NSCLC

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

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 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

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; In press

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 as first-line treatment for advanced *EGFR*-mutated NSCLC. Sixty-eight advanced NSCLC patients were randomized 2:3 to administrate icotinib-alone or chemotherapy plus icotinib. Chemotherapy plus icotinib group showed higher progression-free survival than icotinib alone. Our study suggested that a sequential combination of chemotherapy and EGFR-tyrosine kinase inhibitor is feasible for stage IV *EGFR*-mutated NSCLC patients.

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, for 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 part (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]. Because of the complexity of the EGFR-TKI resistance mechanisms[6-8], 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 might 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 of 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 blood routine test results; (6) expected survival of > 3 mo; (7) negative urine pregnancy test within 7 d before screening for women of child-bearing ages, 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 because of 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 the 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.

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 were presented as means ± SD and medians (ranges). Categorical data were 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 presents 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 of 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 of 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, including 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. Meanwhile, 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 might be a potential strategy for advanced NSCLC with *EGFR* mutation. Yet, the optimal regimen remains to be determined. In this study, icotinib was selected because of a 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 [mOS: 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]. Yet, a phase II clinical study in Japan,

NEJ00, reported that in patients with NSCLC having *EGFR* mutation, the combined therapy of gefitinib, pemetrexed, and carboplatin was significantly superior to chemotherapy followed by target therapy[30]. Among the enrolled 80 patients, 41 received concurrent combination therapy, while 39 also had sequential therapy. The mPFS was 18.3 mo *vs* 15.3 mo [HR = 0.71 (0.42-1.2), *P* = 0.02], and mOS was 41.9 mo *vs* 30.7 mo [HR = 0.51 (0.26-0.99), *P* = 0.042], respectively. The response rates of the two groups were similar (87.8% and 84.6%, respectively). Furthermore, phase II clinical studies conducted in China reported similar results of 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 of 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 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 non-small cell lung cancer[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 of the *EGFR*-mutated subgroup was too small to draw a firm conclusion. The combination therapy may outperform the monotherapy ORR since chemotherapy and TKIs do not affect the cancer cells using the same mechanisms (*i.e.*, hitting the cells through 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 of the sequential treatment group in the present study was superior to that of the TKI-alone therapy group. The reason for the inconsistent results of 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. Because of 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 VEGF 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]. Besides, 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 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]. Still, 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[52,53]. 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 facing 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. It 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. Because of the limited generalizability, the efficacy of the 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 is feasible. No significant differences were found in the influence of the different numbers of chemotherapy cycles or different chemotherapy drugs on the curative effect, suggesting that fewer chemotherapy cycles could bring the same therapeutic effect to these specific patients.

ARTICLE HIGHLIGHTS

Research background

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

Research motivation

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

Research objectives

Some clinical researches 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 by many studies. Therefore, this pilot randomized controlled trial (RCT) aims to evaluate the efficacy and safety of combination therapy than 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

The statistically significant was observed between icotinib alone and chemotherapy + icotinib groups regarding median progression-free survival (P = 0.0249). No statistically significant was found between two and four cycles of chemotherapy which mean a 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, yet, the optimal regimen remains to be determined.

Research conclusions

A sequential combination of chemotherapy and EGFR-TKIs could be a feasible strategy for stage IV EGFR-mutated NSCLC patients suggesting 2-cycle sequentially combination chemotherapy could bring similar effectiveness with 4-cycle sequentially combination chemotherapy on these patients.

Research perspectives

The future studies should involve large population from multicenter around the world to further validate the efficacy and safety for EGFR-mutated NSCLC patients.

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39	Fumihiro Tanaka, Kazue Yoneda, Masaru Takenaka, Koji Kuroda. "Treatment strategy of EGFR-mutated non-small cell lung cancer", Journal of Thoracic Disease, 2022 Crossref	9 words — < 1%
40	Tobias Schupp, Michael Behnes, Mohammad Abumayyaleh, Kathrin Weidner, Kambis Mashayekhi, Thomas Bertsch, Ibrahim Akin. "Angiotensin Converting Enzyme Inhibitors versus Receptor Blockers in Patients with Ventricular Tachyarrhythmias", Journal of Clinical Medicine Internet	9 words — < 1%

41 Wilfried E. Eberhardt. "Randomized multicenter german trial of surgery plus radiotherapy versus tri-modality treatment of operable stage IIIA NSCLC - long-term follow-up results", Journal of Thoracic Oncology, 08/2007
Crossref
9 words — < 1%

42 journals.lww.com
Internet
9 words — < 1%

43 www.koreascience.kr
Internet
9 words — < 1%

44 www.omicsonline.org
Internet
9 words — < 1%

45 NA. "Supplement 2, Proceedings of the 14th World Conference on Lung Cancer, Book 2", Journal of Thoracic Oncology, 2011
Crossref
8 words — < 1%

46 Tudor-Eliade Ciuleanu, Samreen Ahmed, Joo-Hang Kim, Jörg Mezger et al. "Randomised Phase 2 study of maintenance linsitinib (OSI-906) in combination with erlotinib compared with placebo plus erlotinib after platinum-based chemotherapy in patients with advanced non-small cell lung cancer", British Journal of Cancer, 2017
Crossref
8 words — < 1%

47 Won Il Jang, Mi-Sook Kim, Sun Hyun Bae, Chul Koo Cho et al. "High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma", Radiation Oncology, 2013
Crossref
8 words — < 1%

48 Yan Ma, Xiao Ma, Jingting Wang, Shanshan Wu, Jing Wang, Bangwei Cao. "Absolute Eosinophil Count
8 words — < 1%

May be an Optimal Peripheral Blood Marker to Identify Risk of Immune-Related Adverse Events in Advanced Malignant Tumors Treated with PD-1/PD-L1 Inhibitors: A Retrospective Analysis.", Research Square Platform LLC, 2021
Crossref Posted Content

49 rbej.biomedcentral.com
Internet
8 words — < 1%

50 researchonline.lshtm.ac.uk
Internet
8 words — < 1%

51 &NA;, . "Abstracts :", Journal of Thoracic Oncology, 2012.
Crossref
7 words — < 1%

52 David E. Gerber, Leena Gandhi, Daniel B. Costa. "Management and Future Directions in Non-Small Cell Lung Cancer with Known Activating Mutations", American Society of Clinical Oncology Educational Book, 2014
Crossref
7 words — < 1%

53 Masahiro Torasawa, Tatsuya Yoshida, Shigehiro Yagishita, Yukiko Shimoda et al. "Nivolumab versus pembrolizumab in previously-treated advanced non-small cell lung cancer patients: A propensity-matched real-world analysis", Lung Cancer, 2022
Crossref
7 words — < 1%

54 Shao-bo Ke, Hu Qiu, Jia-mei Chen, Wei Shi, Yong-shun Chen. "Therapeutic Effect of First-line Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR-TKI) Combined with Whole Brain Radiotherapy on Patients with EGFR Mutation-positive Lung Adenocarcinoma and Brain Metastases", Current Medical Science, 2018
Crossref
6 words — < 1%

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