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Journal of Virology and Vaccination
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ISSN: 2836-6387 RESEARCH ARTICLE

First-Third generation EGFR inhibitor combined with cytotoxic chemotherapy in elderly Patients with advanced lung adenocarcinoma in routine clinical practice-results from A Subgroup Analysis

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Received: 27 July 2022; **Accepted:** 12 September 2022; **Published:** 26 December 2022.

Citation: An-Tai He, Yi Pei. (2022). First-Third generation EGFR inhibitor combined with cytotoxic chemotherapy in elderly Patients with advanced lung adenocarcinom in routine clinical practice-results from A Subgroup Analysis, Journal of Virology and Vaccination 1(1): DOI: 10.58489/2836-6387/002

Abstract

The third generation Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor (TKI) osimertinib has been initially approved for T790M positive lung adenocarcinoma patients and more recently for first-line treatment of EGFR-mutant T790M negative lung adenocarcinoma, similarly to previous generation TKIs, despite the high response rate, disease progression eventually occurs and current clinical research is focused on novel strategies to delay the emergence of osimertinib resistance. In this study, we investigated as the combination of osimertinib/ gefitinib/ erlotinib with cytotoxic chemotherapy for EGFR-mutated positivelung adenocarcinoma patientsin long-term survivaloutcomes.

Key Words: *lung adenocarcinoma, EGFR inhibitor, Cytotoxic chemotherapy, Osimertinib.*

Materials and Methods

We enrolled Ⅲb-Ⅳ stage lung adenocarcinoma patients with an *EGFR* mutation. Patients receiving standard Osimertinib, Gefitinib, Erlotinip alone treatment and Osimertinib, Gefitinib and Erlotinip with cytotoxic

chemotherapy treatment was retrospectively reviewed. The performance status was collected, the response rate, progression-free survival (PFS) and overall survival (OS) and toxicity profile were analyzed.

Results

Between January 2014 to Dec 2020,240 patients with Ⅲb-Ⅳstages lung adenocarcinoma was enrolled from a institution. All patients who received different standard treatment respectively, were divided into four groups,64 who received (Gefitinib or Erlotinib) with cytotoxic chemotherapy, 60 who received single gefitinib or erlotinib.58 who received (Osimertinib) with cytotoxic chemotherapy,58 who received single (Osimertinib) were eligible for this study. First generation Chemical-TKItherapy group PFS vs First generation TKI therapy alone PFS.P<0.05. Mean Survival Time 22.00-month,95%CI [16.29,27.70] VS

16.00 month.95%CI [11.98,20.01]. First generation Chemical-TKItherapy group OS vs First generation TKI therapy alone OS. P<0.05. Mean Survival Time 32.00-month,95%CI [25.29,3871] VS 28.00-month, 95%CI [14.58,41.41]. Third generation Chemical-TKItherapy group PFS vs Third generation TKI therapy PFS. P<0. 001.Mean Survival Time 40.00,95%CI [28.12,51.87] VS 26.66 95%CI [24.77,29.22]. Third generation Chemical-TKItherapy group OS vs Third generation TKI therapy OS. P<0.05. Mean Survival Time 48.00.95%CI [42.81,53.18] VS 36.00. 95%CI [34.71,38.28]. First-Third generation

Chemical-TKItherapy group PFS vs. First-Third generation TKI therapy alone PFS.P<0.001.Mean Survival Time 28.00,95%CI[24.86,31.11] VS 17.00 95%CI[13.83,20.16].First-Third generation Chemical-TKItherapy group OS vs First-Third generation TKI therapy alone OS.P<0.001. Mean Survival Time 41.00.95%CI [31.70,50.30] VS 29.00. 95%CI [17.68,38.31]. Cox regression models showed a

significant prognostic factors for OS were old age (55-69 years) (HR = 0.49 [0.28–0.89], p < 0.02) and gene mutation (Positive) (HR = 0.15 [0.07–0.29], p < 0.05), First add third generation with chemical therapy (HR = 0.56 [0.35–0.89], p < 0.02).

Conclusion

First-Third generation EGFR inhibitor combined with cytotoxic chemotherapy represents a suitable palliative treatment option in further therapy lines for elderly patients with advanced lung adenocarcinoma. The results obtained under real-life conditions add to our understanding of the benefits and risks of First-Third generation EGFR inhibitor combined with cytotoxic chemotherapy in routine clinical practice.

Background

Lung cancer is the leading cause of cancer deaths worldwide [1], about 85% of cases are diagnosed as non-small-cell lung cancer (NSCLC) [2].The median age of NSCLC patients is 70 years and the disease is

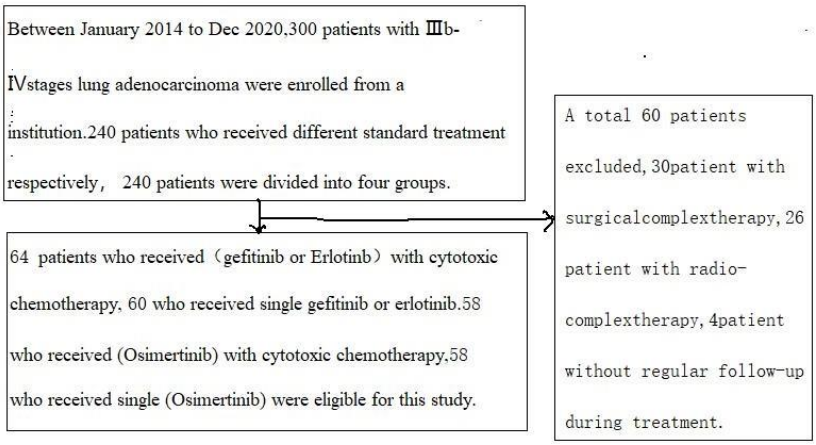
usually diagnosed in advanced stages, when curative surgery is no longer feasible [3]. In metastasized disease, first-line chemotherapy is often not successful and the 5-year survival rate is only 4.2% [3]. NSCLC is histologically classified into the major subtypes adenocarcinoma (~ 40%) [4, 5], Recurring mutations have been reported in genes coding for epidermal growth factor receptors (EGFR) in 10–40% of adenocarcinomas [6,7,8], *EGFR* mutations can lead to constitutive activation of anti-apoptotic and proliferation signaling pathways, which promote cancer progression [9], EGFR tyrosine kinase inhibitors (TKI) are the preferred

first-line treatment for advanced NSCLC with *EGFR* mutations [10, 11], Treating NSCLC is challenging

because of the advanced age of patients. As EGFR-TKI avoid the systemic side effects of traditional chemotherapy, they might be more suitable for treating elderly patients [12]. Osimertinib, a third-generation EGFR-TKI that selectively binds the C797 residue inhibiting the T790M mutation, has shown high activity in term of Progression-Free Survival (PFS) and overall response rate in *EGFR*-T790M positive patients [13, 14] and efficacy superior to gefitinib/erlotinib in the first-line treatment by approximately a 9 months advantage in PFS [15]. However, acquired resistance occurs also to osimertinib either in T790M-positive NSCLC patients or in patients treated in first-line [16,17]. EGFR-dependent or independent mechanisms of resistance have been described even if they remain not completely understood [16]. *EGFR* G796/C797, L792 and L718/G719 mutations, *MET* and *HER2* amplification, *BRAF*, *KRAS*, and *PIK3CA* mutations, oncogenic fusion mutations in *FGFR3*, *RET*, and *NTRK* were recently identified in a large cohorts of osimertinib-resistant lung cancer patients either treated in second-line [18, 19] and in first-line [20].Knowledge of these mechanisms is relevant in order to develop new therapeutic strategies to overcome TKI-resistance; however, how prevent or delay the acquisition of resistance remains an important issue. Some data indicated that in PC9 cell line and xenograft models, the combination of gefitinib with pemetrexed or the intermittent combination of pemetrexed and gefitinib prevented some the appearance of gefitinib resistance mediated by T790M mutation and epithelial-mesenchymal transition [21]; however, the combination was ineffective when gefitinib was administered before pemetrexed. Theoretically, Chemotherapy, given its different and more generic mechanism of action, can postpone the resistance to EGFR-TKIs by limiting the tumor heterogeneity, thus improving the efficacy of treatment either in first-and second-line. Osimertinib combined or intercalated with chemotherapy deserves to be considered either for patients in progression after first/second-generation TKIs or in first-line setting. Our study was undertaken to explore a long-term survival outcome in the combination of osimertinib with pemetrexed add platinum and the combination of gefitinib/erlotinib with pemetrexed add platinum in elderly lung adenocarcinoma patients.

Methods

The flowchart of our study is shown in Fig. 1.



Patients

Methods Between January 2014 and Dec 2020, 240 patients were diagnosed in Shan-Xi Bethune Hospital,Taiyuan City,China.

All patients were aged between 55 and 84 years old. Inclusion criteria were as follows:(1) Pathological diagnosis of lung adenocarcinoma; (2) Karnofsky performance score >60; (3) Adequate organ (white blood cell > 4.0×10/L; neutrophil > 2.0×10/L; hemoglobin > 90 g/L; platelet > 100×10^9/L; aspartate aminotransferase/alanine transaminase < 2.5 upper limit of normal;(4) Routine evaluations were performed on patients, including physical examination,electrocardiography,chest and abdominal computed tomography (CT) with contrast and bone scan.Lung adenocarcinoma-pathology-stages:Ⅲb-IV stages (Table 1

Treatment method:

Table 2. Chemotherapy:(1) pemetrexed plus carboplatin or cisplatin. (2) Docetaxel plus carboplatin or cisplatin.*and so on.*Chemotherapy used for 4 to 6weeks or more.TKI therapy: Before TKI therapy, Tumor gene mutation profile, including EGFRT790M,ALK-M, KRAS-M,METM,,RETM,ROS,*and so on* gene, was performed.If the test was positive,first-generationTKI therapy drugs,Gefitinib, Erlotinib,Ectinib were used.After the first-generation drugs showed resistance,Third-generation TKI therapy drug Osimertinib was used.Eligible patients were randomized to one of the following treatment arms:240 patients divided into 2 group.First group 124patients.60 patients alone Gefitinib group 250 mg/ each 1/ d, or Erlotinip group 150 mg, each 1/ d, oral administration.Oral administration until disease progression.64 patients,Gefitinib/ Erlotinip with chemotherapy group,Chemotherapy regimen:intravenously administered pemetrexed sodium on day 1 of each cycle,500 mg/m2,dose.Cisplatin was given intravenously on days 2,3 and 4, 30 mg /m2,dose or carboplatin on day 1,The doses were 10 mg /m2,One cycle continuous treatment for 4~6 cycles or more.pemetrexed 175 mg/m2,and carboplatin 10 mg /m2, administered intravenously on day.intercalated with Gefitinib 250 mg group or Erlotinip group 150 mg orally on days until progressive disease,or until a discontinuation criterion was met.Second group116 patients,58 patients alone osimertinib group 80 mg/ d,Oral administration until disease progression.58 patients Osimertinib targeted therapy with chemotherapy, Chemotherapy regimen was same as first Group, intercalated with osimertinib group 80 mg/ d,Oral administration until disease progression.

Evaluation:

Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), or progression disease (PD) in accordance with the standard of RECIST [22]. A CR was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A PR was defined as an at least 30% decrease in the sum of the longest diameters of the target lesions for more than 4 weeks without new area of malignant disease. PD indicated an at least 20% increase in the sum of the longest diameter of the target lesions or a new malignant lesion.Stable disease was defined as insufficient shrinkage to qualify for PR and insufficient increase to qualify for PD.An objective response rate (ORR) indicated the proportion of patients achieved CR and PR,while a disease control rate (DCR) indicated the proportion of patients achieved CR, PR and SD.Progression-free survival (PFS) was measured from Day 1 of treatment until the first objective or clinical sign of disease progression.Overall survival (OS) was measured

from Day 1 of treatment until the date of death.Adverse effects including 5 degrees (0-IV) were evaluated following the standard enacted by the World Health Organization in 1981.The follow-up was performed through telephone by the trained investigators with good communication skills and knowledge on the diagnosis. After diagnosed with lung adenocarcinoma, the survival time was determined. After discharge, the patients were inspected every three months in the first one year and there after until death. A series of evaluations were conducted including physical examination, chest radiography, CT/magnetic resonance with the contrast of the metastatic sites, abdominal sonography, PET-CT was considered when necessary.

Statistical analyses:

The incidence of time-to-event data in different subgroups was analyzed using the Kaplan-Meier method and compared with the log-rank test. The potential factors, survival and response data were analyzed overall and in the following subgroups: age (55–69 or ≥ 70 years),*EGFR* mutation (positive or negative) and gender, metastatic lesions1-2 or ≥3.Treatment method（TKI-chemicaltherapy,or TKI therapy alone add

chemical therapy alone).the OS was additionally investigated using Cox regression models (considering single and multiple factors).Multivariable Cox regression analyses were used to estimate the HR and 95% CI for the relationship between the characteristics and overall survival. Statistical analyses were performed using SPSS (Mac ver. 21.0, IBM Corp.).All statistical tests in our study are 2-tailed.A *p*-value of less than 0.05 is considered statistically significant.

Results

Table 1: Patient baseline characteristics (*N* = 240)

Characteristic	No. (%)
Age (yr)	
55-69	152(63.15)
≥ 70	88(36.84)
Gender	
Male	107(44.73)
Female	133(55.26)
Gene mutation (Tested)	
EGFR +	100(41.44)
EGFR -	57(23.68)
Wild-type	5 (1.97)
T790M mutations +	44(18.42)
ALK mutations+	6 (2.63)
KRAS mutations+	13(5.26)
RET mutations+	8(3.28)
MET mutations+	8 (3.28)
EGFR gene mutation site-n	
Exon18	11 (4.76)
Exon19	57(23.80)
Exon19 + Exon21	4(1.58)
Exon 20 +	8(3.17)
Exon21L858	61(25.39)
Chemical-TKI therapy	
Yes	122(50.83)
No	118(49.16)
First-generation Chemical-TKI therapy	64(26.66)
First-third generation Chemical-TKI therapy	58(24.16)
TKI therapy alone	
Yes	118(49.58)
No	122(50.83)
First generation TKI therapy alone	60(25.00)
First-third generation TKI therapy alone	58(24.16)

Table 2: Drugs administered as First generation TKI therapy alone, First generation Chemical-TKI therapy, First-third generation TKI therapy alone, First-third generation Chemical-TKI therapy.

Gefitinib+EtoposideVP16+Cisplatin	*13*	*5.26%*
Gefitinib + Bevacizumab + Cisplatin + Pemetrexed	*10*	*3.94%*
First-third generation TKI therapy alone	*52*	*21.49%*
Type of treatment		
Osimertinib + Gefitinib	*25*	*10.52%*
Osimertinib	*26*	*10.96%*
First-third generation Chemical-TKI therapy	*58*	*24.12%*
Type of treatment		
Osimertinib + Gefitinib + Docetaxel + Carboplatin	*21*	*8.77%*
Osimertinib + Erlotinib + Pemetrexed + Cisplatin	*16*	*6.57%*
Osimertinib + Pemetrexed + Cisplatin	*11*	*4.38%*
Osimertinib + Docetaxel + Carboplatin	*11*	*4.38%*

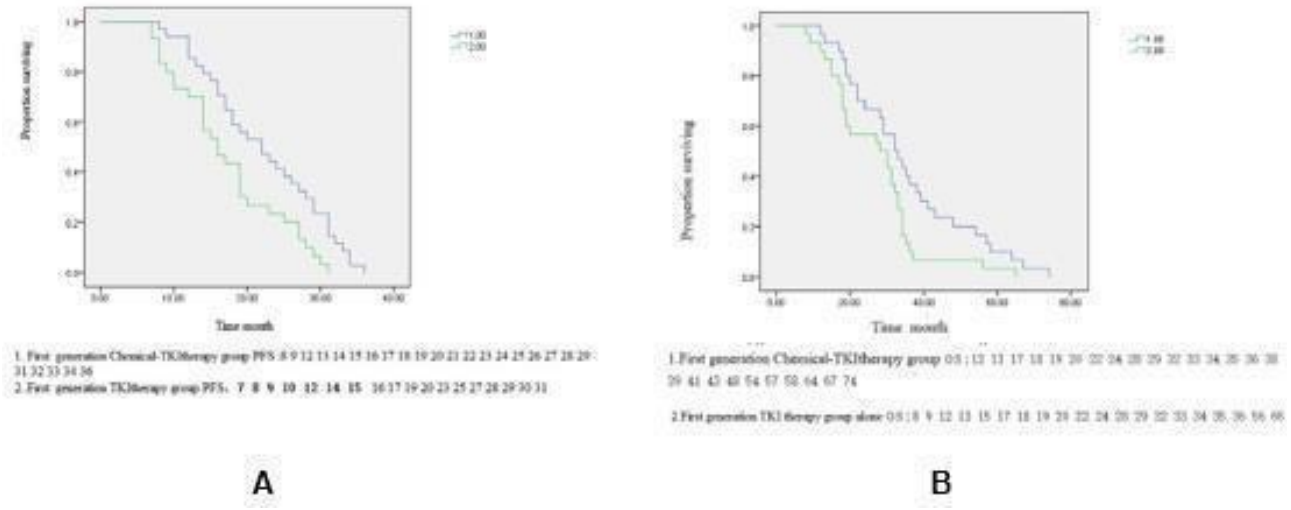
Six or more cycles of chemotherapy were completed in 95% of patients and only one cycle was completed in 4.5% of patient.

Table 3: Results of Cox univariate and multivariate regression analysis

Characteristic	***Univariable analyses (95% CI)***	***Hazard ratio p-value***	***Univariable analyses (95% CI)***	***Hazard ratio p-value***
		Age (yr)		
55-69	*Reference*		*Reference*	
≥70	*0.49(0.30-0.81)*	*0.005*	*0.49 (0.28-0.89)*	*0.02*
		Gender		
Male	Reference		Reference	
Female	0.77(0.53–0.96)	0.04	0.92(0.56-1.53)	0.76
		Gene Mutation		
No	Reference		Reference	
Yes	0.72(0.07-0.25)	0.01	0.15(0.07-0.29)	0.01
		First add third generation TKI therapy with Chemical therapy		
No	Reference		Reference	
Yes	0.56(0.35-0.93)	0.02	1.50(0.42-5.31)	0.52

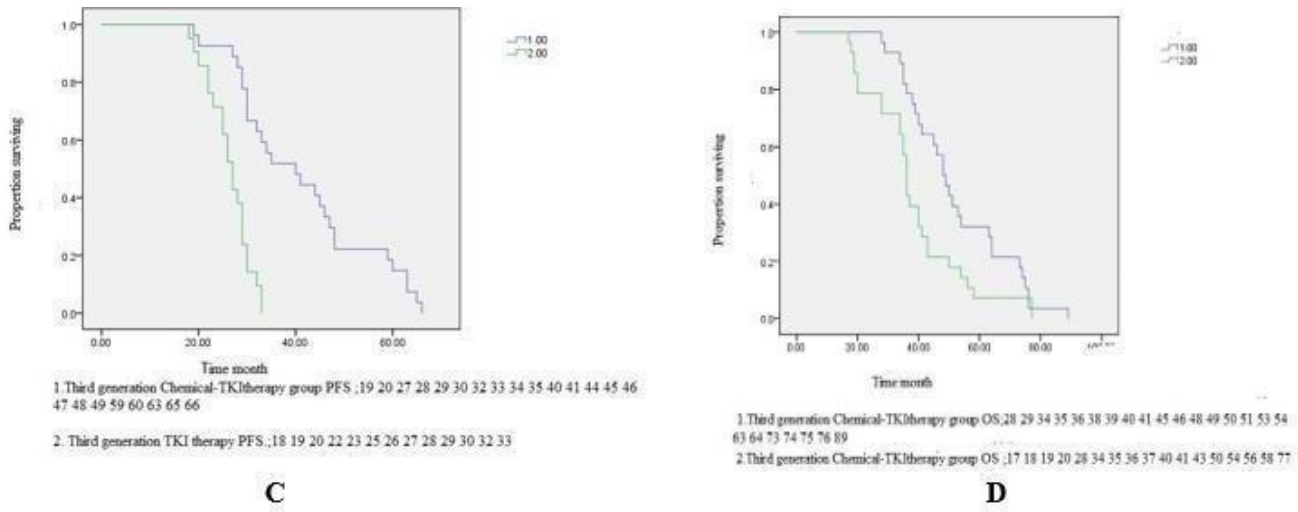
CI. Confidence interval; Cox regression models with adjustment for single factors showed a significant influence of age (yr)(p = 0.005),gender (p = 0.04) and EGFR status (p = 0.01),first add third generation TK therapy with chemical therapy (p = 0.02) on OS. Accordingly, Age (yr) 55-69 had an 51% reduced risk of death compared to≥70 (yr) (hazard ratio([HR] 0.49, 95% CI 0.30–0.81). Females had an almost 30% reduced risk of death compared to males (hazard ratio([HR] 0.71, 95% CI 0.53–0.96). Patients with an EGFR mutation had an almost 28% reduced risk of death compared to negative patients([HR] 0.72,95% CI 0.07-0.25). First add third generation TKI therapy with chemical therapy had an almost 54% reduced risk of death compared to first add third generation TKI

therapy alone.



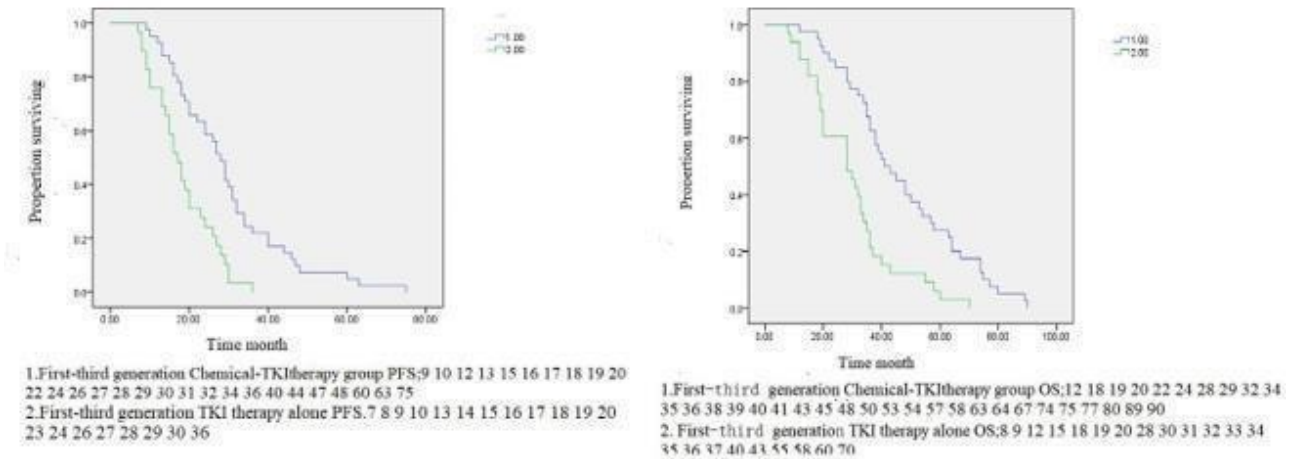
A B

Fig 2 A: First generation Chemical-TKItherapy group PFS vs First generation TKI therapy alone PFS. P<0.05. Mean Survival Time 22.00-month,95%CI [16.29,27.70] VS 16.00-month 95%CI [11.98,20.01]. ***(B)***.First generation Chemical-TKItherapy group OS vs First generation TKI therapy alone OS. P<0.05. Mean Survival Time 32.00-month,95%CI [25.29,3871] VS 28.00-month, 95%CI [14.58,41.41]



C D

Fig 2C: Third generation Chemical-TKItherapy group PFS vs Third generation TKI therapy PFS.P<0.001. Mean Survival Time 40.00, 95%CI [28.12,51.87] VS 26.66, 95%CI [24.77,29.22]. ***(D)*** Third generation Chemical-TKItherapy group OS vs Third generation TKI therapy OS. P<0.05. Mean Survival Time 48.00.95%CI [42.81,53.18] VS 36.00. 95%CI [34.71,38.28].



E F

Fig 2E: First-Third generation Chemical-TKItherapy group PFS vs. First-Third generation TKI therapy alone PFS. P<0.001. Mean Survival Time 28.00,95%CI [24.86,31.11] VS 17.00 95%CI [13.83,20.16]. ***(F)*** First-Third generation Chemical-TKItherapy group OS vs First-

Thirdgeneration TKI therapy alone OS. P<0.001. Mean Survival Time 41.00.95%CI [31.70,50.30] VS 29.00. 95%CI [17.68,38.31].

Table 4: Clinical endpoints and Treatment outcomes:TKItherapy with Chemical-TKLtherapy and TKLtherapyalone stratified by patient baseline characteristics, for the overall patients with Lung adenocarcinoma.

Response N (%)	First generation *Chemical-TKItherapy (N = 64) (%)*	First generation *TKItherapy alone (N = 60) (%)*	p-value	Third generation Chemical- *TKItherapy (N = 58) (%)*	Third generation TKItherapy *alone (N = 58) (%)*	p-value
Partial response (PR)	*45 (70.23)*	*33 (55.23)*		*47 (80.23)*	*43(73.45)*	
Stable disease (SD) ≥ 6 weeks	*21(32.72)*	*12 (20.12)*		*28(48.64)*	*24(41.17)*	
Progressive disease (PD)	*3(5.41)*	*6 (10.34)*		*2(3.11)*	*3(5.12)*	
ORR (CR+PR)	*49 (77.12)*	*29(47.45)*	*<0.05*	*52(89.34*	*44(75.43)*	*<0.05*
DCR (CR+PR+SD)	*54 (84.34)*	*41(67.54)*	*<0.05*	*55(95.34)*	*46 (79.21)*	*<0.05*
Survival time						
PFS, months, median (95% CI)	*22.00 (16.29- 27.70)*	*16.36 (11.98-20.01)*	*<0.001*	*40.00 (28.12-51.87)*	*27.00 (24.78-29.22)*	*<0.05*
OS, months, median (95% CI)	*32.00 (25.29-38.71)*	*28.00 (14.58-41.42)*	*<0.02*	*48.00 (42.81-53.18)*	*36.00 (34.72-50.27)*	*<0.02*

ORR, overall response rate; CR, complete response; DCR, disease control rate; CI, confidence interval; PFS, progression- free survive for treatment; OS, overall survival for treatment.

Table 5: Summary of the most common adverse events for the overall patients with Lung adenocarcinoma.

Summary of the most common adverse events for the overall patients with Lung adenocarcinoma. Adverse event with AE (Grade 1-4)	First generation Chemical-TKItherapy (N = 64) (%) All grade	First generation TKItherapy alone (N = 60) (%) All grade	Third generation Chemical-TKItherapy (N = 58) (%)All grade	Third generation TKItherapy alone(N = 58) (%) All grade
Skin rash	*40 (63.12)*	*37(61.48)*	*34(58.32)*	*31(53.02)*
Anorexia	*34(53.12)*	*25(42.21)*	*25 (42.43)*	*18 (31.81)*
Cough	*30(46.12)*	*25(40.23)*	*21 (36.23)*	*19(33.31)*
Nausea	*28(43.12)*	*18(30.23)*	*18(30.12)*	*14(24.21)*
Fatigue	*19 (29.09)*	*17(27.58)*	*9 (15.13)*	*6(10.61)*
Diarrhea	*30(47.12)*	*26(43.34)*	*24 (41.12)*	*18(31.81)*
Neutropenia	*21 (32.12)*	*16(27.12)*	*15 (26.12)*	*11(18.22)*
Anemia	*28 (43.00)*	*21(35.12)*	*19 (32.12)*	*16(27.31)*
Thrombocytopenia	*26(40.07)*	*19(32.12)*	*19 (32.12)*	*16 (27.31)*
Increased LFT	*35 (54.54)*	*25(41.72)*	*11(18.13)*	*8(13.61)*
Mucositis	*12 (18.18)*	*12(20.68)*	*9(15.23)*	*0(0.00)*

AE adverse event; Gr grade; N number, LFT liver function test

During the study,794 AEs were observed in 240 patients (Table 5). According to the common toxicity criteria for adverse events (CTC), The most commonly reported AEs were rash and anorexia diarrhea followed by increased LFT, cough,nausea, anemia and neutropenia. Most of the toxicity was grade 1 to 2, and remitted after treatment. The frequency of AEs was not significantly affected by age or *EGFR* mutation status (data not shown). All AEs reported were consistent with those described in the summary of product characteristics [23].

Discussion

The study was designed to evaluate the effect of intercalation therapy with gefitinib or erlotinib or osimertinib with platinumar add pemetrexed chemotherapy. Our first-generation target group includes gefitinib, erlotinib. The study demonstin relation to PFS, and OS.Toxicity profiles were generally clinically tolerable. In another studies are same[21-25],the sequence-dependent synergism between platinumar add pemetrexed and gefitinib was demonstrated in human lung cancer cell lines with both wild-type and mutant EGFR genes [26].The concurrent regimen is currently being evaluated against gefitinib alone in a randomized phase III study recently presented at ESMO 2018 meeting [2].In this trial, the patients who received a combination of gefitinib with carboplatin-pemetrexed showed a statistically significant benefit in survival (PFS of 20.9 vs 11.2 months, $p < 0.001$ and OS of 52.2 vs 38.8, $p = 0.013$ for gefitinib and carboplatin/pemetrexed and for gefitinib alone, respectively).Several later phase I/II clinical studies showed that an intercalated

regimen of chemotherapy and EGFR TKI were safe and effective [25–28, 29].WSW clinical studies reported that the intercalated regimen offered superior efficacy compared to chemotherapy or EGFR TKIs alone [30, 31]. In a three-arm phase II study,The combination was suggested as a new treatment option for patients with unknown EGFR status in a previous clinical study [30],Although molecular tests are used routinely in clinical practice, EGFR status remains unknown in certain patients.We think that the intercalated strategy could be effective in patients with wild-type or unknown EGFR status.According to several clinical studies, Intercalated treatment might be a promising approach for patients with lung adenocarcinoma with EGFR mutant disease or selected patient with unknown EGFR mutation status, [30–32].Our results are first generation Chemical-TKItherapy group PFS vs first generation TKI therapy alone PFS. P<0.05. Mean Survival Time PFS 20.03,95%CI[17.55,22.50] VS 16.36 95%CI[13.59,19.13],

First generation Chemical-TKItherapy group OS vs First generation TKI therapy alone OS. P<0.01. Mean Survival Time OS 37.16,95%CI[32.08,42.23] VS 26.66 95%CI[19.09,34.24]. First generation

Chemical-TKItherapy group vs First generation TKI therapy alone had a stronger effect on ORR and DCR. Osimertinib is a third-generation EGFR TKI,A large rando mized trial comparing osimertinib to gefitinib or erlotinib reported that PFS was significantly longer in the osimertinib arms, and time to CNS metastases was significantly delayed because osimertinib crosses the blood-brain barrier.[33] Toxicity rates were lower with osimertinib than the first-generation inhibitors and the HRs for benefit were similar in younger and older patients. Similarly to previous generation TKIs, despite the high response rate, disease progression eventually occurs and current clinical research is focused on novel strategies to delay the emergence of osimertinib resistance. Although preclinical and clinical researches have explored the

interaction of first-generation EGFR-TKIs and cytotoxic agents [34,35,36,29,30,31,32], to date there are no data on clinical combination of chemotherapy with third-generation EGFR-TKIs, suc as osimertinib. In this study, we explored the efficacy of osimertinib combined with pemetrexed add platinumar in lung adenocarcinoma. A strong anti-tumor effect was observed when osimertinib was combined with pemetrexed add platinumar intercalated, By contrast osimertinib monotherapy. We strongly indicating that the addition of chemotherapy may potentiate the efficacy of osimertinib either in term of inhibition of tumor growth or appearance of relapses. Figure2C. 1Third generation Chemical-TKItherapy group PFS vs Third generation TKI monotherapy PFS. P=0.005. Mean Survival Time 40.73,95%C I[33.56,47.90] VS 26.66 95%CI[22.89,30.44].Figure2D.1.Third generation Chemical-TKItherapy group OS vs Third generationTKI monotherapy OS. P=0.04.Mean Survival Time 54.00,95%CI[45.81,62.18] VS 39.72 95%CI[29.18,50.27].Table 4.Third generation Chemical-TKItherapy group vs Third generation TKI therapy alone had a stronger effect on ORR and DCR.In a mouse model of PC9T790M xenograft tested in vitro,A strong anti-tumor effect was observed when osimertinib was combined with pemetrexed or cisplatin intercalated with osimertinib alone, no tumor became resistant, differently from the treatment with osimertinib alone which induced acquired resistance in 50% of mice.The combination treatment enhanced the percentage of fibrotic tissue within the xenograft tumors and the small tumors did not regrow when the administration of drugs was stopped, indicating a stronger efficacy in eradicating parenchymal tumor cells [39]. In PC9 and PC9T790M cell lines, analysis of signaling transduction pathways and protein related to cell death revealed that the combination treatment did not affect the intracellular transduction pathways, which were already completely suppressed by osimertinib alone,but strongly enhanced apoptosis signaling via caspase-7 activation. This observation may be of relevance for the results obtained in vivo. therefore, the selective pressure exerted by TKIs may promote the clonal expansion of resistant clones through different molecular mechanismsresults [37,38]. Our also provide a strong rationale for randomized studies comparing osimertinib monotherapy vs osimertinib plus chemotherapy, either in *EGFR* T790M positive and negative in EGFR-TKI naïve NSCLC patients. A phase III trial evaluating osimertinib combined with platinum-pemetrexed vs osimertinib monotherapy could be the right step forward to significantly prolong the survival of *EGFR*-mutated NSCLC patients[40].Combination cisplatin/carboplatin plus pemetrexed is the standard treatment regimen for advanced nonsquamous NSCLC and has been frequently used as the backbone of combination treatment[41,42,43].After eradicating tumors with heterogeneity, adding chemotherapy to osimertinib might increase the response rate and improve PFS

and OS with a low incidence of grade ≥ 3 AEs [44],Table5.For each of these AEs,the majority of Osimertinib with carboplatin-pemetrexed chemotherapy were grade 2 or 3 in severity, mild toxicities including skin rash(58.32%),anorexia(42.43%),nausea(31.12%),diarrhea(41.12%),cough(36,23%),anemia(32.12%), thrombocytopenia (32.12%) events. Less than the common adverse effects of first generation Chemical-TKItherapy group. Our Cox multivariate analysis also showed that age ≥70 years (in contrary to 55-69 years),mutation of genes positive compared to negative),Females compared to males, TKItherapy with chemical therapy compared to TKItherapy alone and chemical therapy alone all were significant prognostic factors.seeTable3.A large phase-3 trial with erlotinib including 586 younger and 163 elderly patients demonstrated a similar survival and quality of life (QoL) in both age groups, although a somewhat higher toxicity in the elderly was observed [45]. Clinical studies examining the elderly population are limited and often firm conclusions cannot be drawn [46,47].In accordance with previous findings, females treated with erlotinib lived longer than males [48,49].OS was significantly better in females than males ($p = 0.04$).Gene mutation improved survival time in patients. Lung adenocarcinoma with EGFR mutations was found to be 41.44% in this study. Recurring mutations have been reported in genes coding for epidermal growth factor receptors (EGFR) in 10–40% of adenocarcinomas [50,51,52], The mutant patients had a longer overall survival (OS) than the wild-type patients[54],Our patient with positive EGFR gene mutations demonstrated a longer progress-free OS survival than those with negative and wild-type gene.

Nevertheless,EGFR mutations were more frequent in patients over 75 than in younger patients:17% versus 8.1% (P<0.0001)[55]. The prognostic factors found in this study also included First add third TKItherapy with chemicaltherapy group had a longer OS survival time than the monotherapy TKI therapy or chemical therapy alone.For lung adenocarcinoma,chemical-TKI therapy was identified to be a good treatment option.Most limitations of our study relate to the nature of a non-interventional trial,The number of patients hampered the comparison of third generation Chemical-TKItherapy group effectiveness in a larger group of patients with or without *EGFR* mutations.The high rate of treatment discontinuations due to the severely ill patient population might have had an influence on data analysis and interpretation. Furthermore,The results of post-hoc analyses have to be interpreted with caution. Nevertheless,Our observational study generated invaluable results for real-life treatment decisions.

Conclusion

First-Third generation EGFR inhibitor combined with cytotoxic chemotherapy represents a suitable palliative treatment option in further therapy lines for elderly patients with advanced lung adenocarcinoma. The results obtained under real-life conditions add to our understanding of the benefits and risks of First-Third generation EGFR inhibitor combined with cytotoxic chemotherapy in routine clinical practice.

Abbreviations

NSCLC: Non-small-cell lung cancer

EGFR： Epidermal growth factor receptors

TKIs: Tyrosine kinase inhibitors

AE: Adverse event

CI: Confidence interval

DCR: Disease control rate

ORR: Objective response rate

CR: Complete response

PR: Partial response,

SD: Stable disease

PD: Progression disease

HR: Hazard ratio

OS: Overall survival

PFS: Progression-free survival

QoL: Quality of life

Declarations

1. Ethical Statement

All patients signed informed consent before treatment, including their consent to treatment and clinical information for further prognostic factors analysis. This study was approved by the Research Ethics Committee of Shan-Xi Bethune Hospital, Taiyuan City, Shanxi Province, China

1. **Consent for publication**

We would like to submit the enclosed manuscript entitled “First-Third generation EGFR inhibitor combined with cytotoxic chemotherapy in elderly Patients with advanced lung adenocarcinom in routine clinical practice-results from A Subgroup Analysis. we wish to be considered for publication in this Journal, No conflict of interest exits in the submission of this manuscript, and manuscript is

approved by all authors for publication. We would like to declare on behalf of our co-authors that the work described was original research that has not been published previously and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the manuscript that is enclosed.

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Availability of data and material

Availability of data and material : All data, models, and code generated or used during the study appear in the submitted article.

The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study

Competing interests, Funding

This research received no grant from any funding agency in the public commercial or not-for profit sectors. The authors declare that there is no conflict of interest

Authors' contributions

Chen, contributed to the conception of the study; He, performed the experiment; Chen, He, contributed significantly to analysis and manuscript preparation; He, performed the data analyses and wrote the manuscript; Yi Pei, helped perform the analysis with constructive discussions. Acknowledgements Firstly, I would like to give my sincere gratitude to Prof.fu-bin Qiou my tutor who, with extraordinary patience and consistent encouragement, gave me great help by providing me with necessary materials, advice of great value and inspiration of new ideas. It is his suggestions that draw my attention to a number of deficiencies and make many things clearer. They graciously make considerable comments and sound suggestions to the outline of this paper. It is of great help for me to finish this thesis successfully.

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