FIRST-LINE CHEMOTHERAPY OUTCOMES IN A PATIENT WITH RELAPSED METASTATIC NON-SMALL CELL LUNG CANCER HARBORING AN EGFR EXON 20 INSERTION MUTATION

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ABSTRACT

Introduction: Non-small cell lung cancer (NSCLC) with exon 20 insertion mutations accounts for 4-10% of all NSCLC patients with EGFR mutations. The primary treatment for NSCLC patients with recurrent metastatic EGFR exon 20 insertion mutations remains platinum-based doublet chemotherapy. However, there are very few studies in Vietnam evaluating the effectiveness of this treatment. Therefore, this study was conducted to evaluate the effectiveness of this therapy in the mentioned patient group.

Subjects and Methods: This is a retrospective cross-sectional descriptive study on 36 NSCLC patients with recurrent metastatic EGFR exon 20 insertion mutations treated with platinum-based doublet chemotherapy from January 2019 to June 2024 at Vietnam National Cancer Hospital to evaluate treatment outcomes and adverse effects of the regimen in this patient group.

Results: The response rate of the regimen was 25%, and the disease control rate was 66.7%. The median progression-free survival (PFS) was 7.0 months. The median overall survival (OS) was 17.6 months. The majority of patients experienced at least one adverse effect, accounting for 80.6%. The most common adverse effects were neutropenia (in 58% of patients), peripheral neuropathy (44%), anemia (48%), and nausea (42%). The most common grade 3 or higher adverse effects were neutropenia (25%), thrombocytopenia (6%) and anemia (8%). Dose reductions and drug discontinuations due to adverse effects were reported in 17% and 8% of patients, respectively.

Conclusion: First-line treatment with platinum-based doublet chemotherapy for recurrent/metastatic NSCLC patients with exon 20 insertion mutations is an effective treatment method with manageable toxicity.

Keywords: Non-small cell lung cancer; EGFR exon 20 insertion; platinum-based doublet chemotherapy.

I. INTRODUCTION

Lung cancer (LC) is the most common malignancy and the leading cause of cancer-related mortality worldwide. Non-small cell lung cancer (NSCLC) accounts for the majority (85%) of all primary lung malignancies. The epidermal growth factor receptor (EGFR), a member of the human epidermal receptor (HER) family, plays a vital role in cellular proliferation, metabolism, and evasion of apoptosis. EGFR exon 20 insertion mutations (EGFRex20ins) comprise approximately 4% to 10% of EGFR-mutated NSCLC and about 2% of all NSCLC cases. These mutations are more frequently observed in females, non-smokers or light smokers,

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Date received: 22/3/2025
Date reviewed: 03/4/2025
Date accepted for publication: 10/4/2025

and are typically associated with adenocarcinoma histology. EGFRex20ins is also characterized by a high rate of initial brain metastases and a pattern of bone metastasis similar to that seen with classical EGFR-activating mutations.

Over the past 20 years, EGFR tyrosine kinase inhibitors (EGFR-TKIs) have become an effective treatment option for NSCLC patients harboring EGFR mutations. However, unlike common EGFR mutations, EGFRex20ins responds poorly to first- and second-generation EGFR-TKIs such as afatinib, erlotinib, and gefitinib, with response rates around 10% and a median progression-free survival (PFS) of only 1 to 3 months. Even when osimertinib was administered at a doubled dose (160 mg instead of 80 mg) in a study involving 21 patients previously treated with EGFR-TKIs, outcomes were still suboptimal: the objective response rate was 25%, median PFS was 9.7 months, and median duration of response was 5.7 months. Similarly, immune checkpoint inhibitors, either as monotherapy or in combination with chemotherapy, have shown poor efficacy in patients with EGFRex20ins, with response rates ranging from 0% to 25% and median PFS of only 2 to 3 months. The monoclonal antibody amivantamab, in combination with platinum-based chemotherapy, has demonstrated improved survival in NSCLC patients harboring EGFRex20ins. However, this drug has not yet been approved by the Ministry of Health in Vietnam.

Therefore, for most patients with relapsed or metastatic NSCLC carrying EGFRex20ins mutations, platinum-based chemotherapy remains the standard treatment option. However, in Vietnam, clinical research on treatment outcomes in this patient group remains limited. Therefore, we conducted this study with two objectives:

- To evaluate the outcomes of first-line chemotherapy in patients with relapsed or metastatic NSCLC harboring EGFR exon 20 insertion mutations.

- To assess the adverse effects of this treatment regimen in the study population.

2. SUBJECTS AND METHODS

2.1. Subjects

This study included 36 patients diagnosed with relapsed or metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion mutations, who received first-line platinum-based doublet chemotherapy at Vietnam National Cancer Hospital from January 2019 to June 2024.

Inclusion Criteria:

- Confirmed diagnosis of relapsed/metastatic NSCLC according to AJCC 8th edition.

- Presence of EGFR exon 20 insertion mutation, without accompanying mutations, as determined by next-generation sequencing (NGS) or Real-time PCR using the Cobas EGFR Mutation Test v2.

- Measurable lesions on imaging (MRI, CT scan). Patients with asymptomatic or stable brain metastases after treatment were also eligible.

- Received at least 2 and up to 6 cycles of platinum-based doublet chemotherapy.

- Age > 18 years, any sex, with an ECOG performance status (PS) of 0 or 1.

- Adequate organ function: White blood cell count (WBC) ≥ 4 G/L; Platelet count (PLT) ≥ 100 G/L; Hemoglobin ≥ 100 g/L; AST/ALT ≤ 2× upper limit of normal (ULN); Total bilirubin ≤ 1.5× ULN; Creatinine ≤ 1.5× ULN; Complete and accessible medical records.

Exclusion Criteria:

- Patients with a second primary malignancy.

- Contraindications to treatment drugs, such as severe liver or kidney dysfunction or drug hypersensitivity.

- Uncontrolled brain metastases.

- Patients who had received treatment for metastatic disease prior to the study.

- Patients unwilling to cooperate or lost to follow-up.

2.2. Methods

- Study design: Retrospective cross-sectional descriptive study.

- Study period and location: From January 2019 to June 2024 at Vietnam National Cancer Hospital.

- Sampling method: Convenience sampling; 36 eligible patients were included.

- Data Collection:

+ Clinical and paraclinical information collected included: Age, sex, reason for admission, smoking status, performance status, tumor characteristics, lymph node involvement, metastatic sites, histopathological type, and EGFR mutation testing method.

+ Overall Response Rate (ORR): Percentage of patients achieving partial or complete response; Disease Control Rate (DCR): Percentage of patients with complete response, partial response, or stable disease; Progression-Free Survival (PFS): Time from study enrollment to disease progression or death from any cause; Overall Survival (OS): Time from enrollment to death from any cause.

+ Treatment toxicity: Hematologic, hepatic, renal, gastrointestinal toxicities were assessed according to CTCAE version 4.0.

- Study Procedure:

+ Step 1: Select patients based on inclusion criteria.

+ Step 2: Collect clinical and laboratory data.

+ Step 3: Administer chemotherapy regimens: Pemetrexed 500 mg/m² + Carboplatin AUC 5, every 3 weeks; or Paclitaxel 200-225 mg/m² + Carboplatin AUC 6, every 3 weeks.

+ Step 4: Evaluate treatment outcomes: Tumor response assessed using RECIST 1.1 (2009), Survival analysis using the Kaplan Meier method, Toxicity assessed per CTCAE v4.0. Patients were evaluated every 2–3 cycles or earlier if abnormalities were noted.

- Data Analysis:

Data were entered and analyzed using SPSS version 22.0. Descriptive statistics (percentages, means, standard deviations) were used. Survival estimates were calculated using the Kaplan Meier method.

2.3. Ethical considerations

All patients in the study voluntarily participated. The study was conducted solely for the purpose of improving treatment quality, with no other objectives. Patients who met the inclusion criteria were thoroughly and clearly informed about available treatment options, the treatment process, advantages and disadvantages of each regimen, and potential risks. All personal and medical information was kept strictly confidential.

3. RESULTS

3.1. Clinical characteristics of the study population

Table 1. Characteristics of the study population

Characteristic	Number of Patients (n)	Percentage (%)
Age		
Mean age: 59,61		
> 65 years	12	33,3
≤ 65 years	24	66,7

Characteristic	Number of Patients (n)	Percentage (%)
Gender		
Male	28	77,8
Female	8	22,2
Smoking History		
Non-smokers	10	27,8
Smokers	26	72,2
ECOG		
0	19	52,8
1	17	47,2
Histology		
Adenocarcinoma	33	91,7
NSCLC, NOS	3	8,3
EGFR testing method		
PCR	13	36,1
NGS	23	63,9
Metastatic sites		
Brain	13	36,1
Lung	8	22,2
Pleura	12	33,3
Liver	3	8,3
Bone	18	50
Adrenal gland	6	16,7
Chemotherapy regimens		
Pemetrexed - carboplatin	19	52,8
Paclitaxel - carboplatin	17	47,2
Number of chemotherapy cycles		
2 cycles	6	16,7

Characteristic	Number of Patients (n)	Percentage (%)
3 cycles	5	13,9
4 cycles	10	27,8
5 cycles	4	11,1
6 cycles	11	30,6

Remarks: The average age of the study population was 59.61 years; the male-to-female ratio was 3,5/1. A majority of patients had a history of smoking (72.2%). ECOG performance status 0 was the most common (52.8%). Bone was the most frequent metastatic site (50%), followed by brain metastases (36.1%). Liver metastases were the least common (8.3%). Adenocarcinoma was the most prevalent histological type (91.7%). The most commonly used chemotherapy regimen was pemetrexed - carboplatin (52.8%). NGS was the most frequently used EGFR testing method (63.9%).

3.2. Treatment outcomes

Table 2. Treatment response

Treatment response	Number of patients (n) and percentage (%)	Paclitaxel-carboplatin	Pemetrexed-carboplatin
Complete Response	0 (0)	0 (0)	0 (0)
Partial Response	9 (25)	3 (17,6)	6 (31,6)
Stable Disease	15 (41,7)	8 (47,1)	7 (36,8)
Progressive Disease	12 (33,3)	6 (35,3)	6 (31,6)

Remarks: The overall response rate (ORR) was 25%. The disease control rate (DCR) was 66.7%. The response rate for the paclitaxel-carboplatin regimen was 17.6%, while for the pemetrexed-carboplatin regimen it was 31.6%.

Observation: The median progression-free survival time is 7 months. The shortest progression-free survival time is 2 months, while the longest is 27 months.

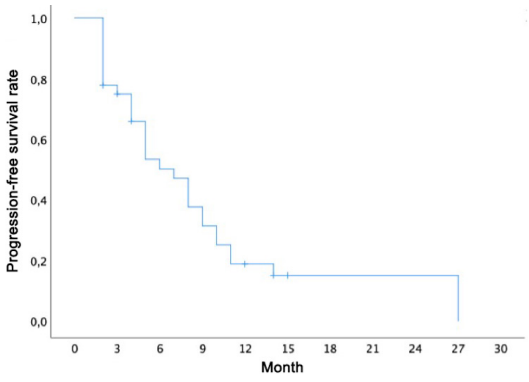

Figure 1. Progression-Free survival time

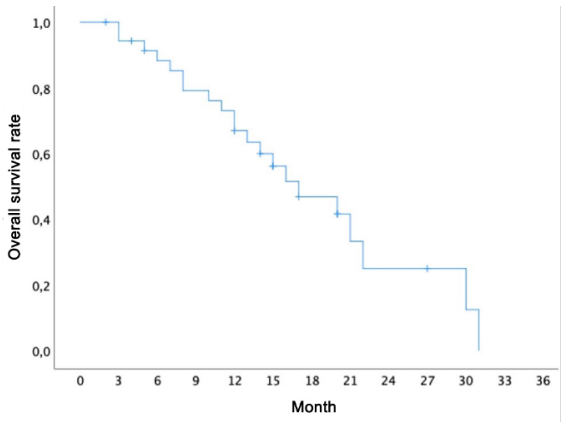

Figure 2. Overall Survival Time

Observation: The median overall survival time is 17 months. The shortest overall survival time is 3 months, and the longest is 31 months.

3.3. Adverse effects of the treatment regimen

Table 3. Adverse effects of the treatment regimen

Adverse Effect	All Grades	Grade ≥ 3
Leukopenia	58% (n=21)	25% (n=9)
Anemia	38% (n=14)	8% (n=3)
Thrombocytopenia	36% (n=13)	6% (n=2)
Vomiting	22% (n=8)	0% (n=0)
Nausea	42% (n=15)	0% (n=0)
Fatigue	17% (n=6)	0% (n=0)
Elevated AST	36% (n=13)	0% (n=0)
Elevated ALT	36% (n=13)	0% (n=0)
Elevated Creatinine	14% (n=5)	0% (n=0)
Peripheral Neuropathy	44% (n=16)	6% (n=2)
Dose reduction due to toxicity	17% (n=6)	
Discontinued due to side effects	8% (n=3)	

Observation: The majority of patients (80.6%) experienced at least one adverse effect. The most common side effects were leukopenia (58%) and peripheral neuropathy (44%), followed by anemia (38%) and nausea (42%). The most frequent grade ≥ 3 toxicities were leukopenia (25%) and anemia (8%). Dose reduction and treatment discontinuation due to toxicity occurred in 17% and 8% of patients, respectively.

4. DISCUSSION

In our study, the average age was 59.61 years. The majority of patients were under 65 years old, accounting for 66.7%. Most patients were male (77.8%). Adenocarcinoma was the predominant histological subtype, found in 91.7% of patients. Bone, brain, and pleura were the most common sites of metastases, accounting for 50%, 36.1%, and 33.3%, respectively. The most commonly used chemotherapy regimen was pemetrexed–carboplatin, administered to over half of the patients, and nearly one-third of patients underwent up to 6 treatment cycles. The characteristics of our patient population show both similarities and differences compared to other studies. Most studies indicate that patients with EGFR exon 20 insertions (EGFRex20ins) are generally 60 years old or younger. Caicun and colleagues reported a mean age of 61, with most patients being under 65 (63%)[5]. Similarly, in Morita's study, the median age was 60[6]. In Shah's study, the figure was also 60 [7]. Clearly, EGFRex20ins seems to occur more commonly in a younger population. However, our study shows a reversed gender distribution, with males being predominant. This contrasts with other studies where exon 20 insertions are more frequently found in females[5,6]. This discrepancy might be due to the small sample size in our study, which may not fully represent the population of NSCLC patients with EGFR exon 20 insertion mutations. Regarding metastatic sites, in our study, EGFRex20ins tended to spread to the bone, brain, and pleura. According to Morita's study, bone metastases (21.6%) were the most common among patients with exon 20 insertions, followed by the central nervous system (CNS) (13.0%) and liver (17.4%)[6]. In a study conducted in China, Yang also reported that bone and lung were the most common metastatic sites, accounting for 40.6% and 40%, respectively, followed by pleura and brain at 36.4% and 23%[8].

In terms of chemotherapy, more than half of our patients received pemetrexed-platinum-based regimens. A multicenter study by Su demonstrated that patients treated with pemetrexed-based chemotherapy had a longer median progression-free survival (PFS) compared to those who did not (5.5 vs. 3.0 months, p = 0.0026)[9]. Data from 66 patients showed a median overall survival (OS) of 24.7 months. Patients receiving pemetrexed-based chemotherapy tended to have longer OS than those who did not (25.0 vs. 19.6 months, P = 0.0769)[9]. However, for advanced NSCLC in general, paclitaxel carboplatin and pemetrexed carboplatin regimens produce similar outcomes, although pemetrexed-based regimens tend to be better tolerated[10]. Our study showed an objective response rate (ORR) of 25% and a disease control rate of 66.7%. The PFS was 7.0 months, and OS was 17 months. In a retrospective study at Stanford University, the objective response rate to platinum doublet chemotherapy was 44% (8 partial responses, 10 stable disease), with an average tumor burden reduction of 22% (SD: 15.6). PFS was 7.1 months (95% CI, 6.3–13.7)[7]. A Japanese study on 85 patients with exon 20 insertions showed that pemetrexed-containing regimens provided better PFS (6.2 vs. 2.7 months, p < 0.0001) and OS (28 vs. 13.9 months, p = 0.016) compared to non-pemetrexed regimens[10]. According to Morita's study, the ORR and median PFS of first-line platinum chemotherapy in patients with exon 20 insertions were 11.8% (95% CI: 1.5–36.4) and 8.9 months (95% CI: 5.0–17.3), respectively [6]. Compared to other treatment approaches, a recent study comparing chemotherapy versus chemotherapy plus amivantamab in NSCLC patients with EGFRex20ins found significantly longer PFS in the amivantamab-combination group (HR = 0.40; 95% CI: 0.30 to 0.53; P < 0.001)[5]. After 18 months, PFS was observed in 31% of patients receiving amivantamab-combination therapy, compared to 3% in the chemotherapy-only group. PFS was 12.9 months (95% CI: 11.4–16.7) for the combination group versus 6.9 months (95% CI: 6.2–8.3) in the chemo-only group (HR = 0.38; 95% CI: 0.29–0.51). Objective responses were reported in 73% (95% CI: 65–80) of the combination group and 47% (95% CI: 39–56) of the chemo-only group (RR = 1.50; 95% CI: 1.32–1.68; P < 0.001)[5].

Our study found that most patients experienced at least one adverse event. The most common adverse events were neutropenia (58%), peripheral neuropathy (44%), anemia (38%) and nausea (42%). The most frequent grade ≥3 adverse events were neutropenia (25%), thrombocytopenia (6%), and anemia (8%). Adverse events led to dose reductions in 17% of patients and treatment discontinuation in 8%. These results are consistent with previous studies. One study on EGFRex20ins also showed that most patients experienced at least one adverse event. The most commonly reported events were anemia (55%), neutropenia (45%), and nausea (42%) in the chemotherapy group. Febrile neutropenia occurred in 2% of patients receiving chemotherapy. The most frequent grade 3 toxicities were neutropenia (23%), anemia (12%) and thrombocytopenia (10%). Serious adverse events occurred in 31% of patients in the chemotherapy group. Adverse events leading to dose interruption, dose reduction, and discontinuation occurred in 36%, 23% and 10% of patients, respectively. Death within 30 days after the last dose of study drug occurred in 4 patients (3%) [5]. Compared to advanced-stage NSCLC patients treated with paclitaxel carboplatin, serious adverse events leading to hospitalization occurred in 13.1% of patients. The rates of peripheral neuropathy, nausea and vomiting, and hematologic toxicity were 69.9%, 44.3%, and 67.1%, respectively. Interstitial lung disease occurred in 8 patients receiving paclitaxel carboplatin (1.4%), one of whom died[5].

5. CONCLUSION

Based on our study of 36 patients with advanced recurrent metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion mutations who received first-line platinum-based

doublet chemotherapy at Vietnam National Cancer Hospital from January 2019 to June 2024, we conclude the following:

- The objective response rate (ORR) of the regimen was 25%, and the disease control rate (DCR) was 66.7%.

- The median progression-free survival (PFS) was 7.0 months.

- The median overall survival (OS) was 17.6 months.

- Most patients experienced at least one adverse event, the most common being neutropenia (58%), peripheral neuropathy (44%), anemia (48%) and nausea (42%). The most frequent grade ≥3 adverse events were neutropenia (25%), thrombocytopenia (6%), and anemia (8%). Dose reductions and treatment discontinuations due to toxicity occurred in 17% and 8% of patients, respectively.

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