ORIGINAL RESEARCH

The effect of icotinib combined with chemotherapy in untreated non-small-cell lung cancer that harbored EGFR-sensitive mutations in a real-life setting: a retrospective analysis

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Purpose: This study was conducted to compare the efficacy of a combination of icotinib and chemotherapy with icotinib or chemotherapy alone in untreated non-small cell lung cancer (NSCLC) patients harboring epidermal growth factor receptor (EGFR)-sensitive mutations and to analyze the curative effect of different treatments on different genetic mutations (EGFR 19 exon deletion and L858R mutation) in a real-life setting.

Patients and methods: One hundred ninety-one patients were studied in this retrospective analysis from January 2013 to December 2015. The baseline characteristics, curative effects and adverse events of patients were analyzed. The primary endpoint was progression free survival (PFS).

Results: Longer PFS and overall survival (OS), and better objective response rate (ORR) were observed in the combination group compared to icotinib or chemotherapy along. For patients with an EGFR 19 exon deletion, the PFS, OS, and ORR in the combination group were superior to those in the icotinib or chemotherapy group. For the patients with the EGFR L858R mutation, better PFS and ORR were observed in the combination group, but OS was not obviously prolonged. Grade 3 or 4 adverse events were most commonly reported with combination therapy or chemotherapy alone. No possible drug-related interstitial lung disease or of drug related deaths occurred.

Conclusion: The combination of icotinib and chemotherapy in patients with untreated NSCLC harboring sensitive EGFR mutations resulted in improved PFS and OS,especially in those who harbored the EGFR exon 19 deletion.

Keywords: non-small-cell lung cancer, EGFR-TKI, icotinib, chemotherapy, first-line treatment

Introduction

Lung cancer is the leading cause of cancer mortality worldwide, with ~80%–85% patients suffering from non-small-cell lung cancer (NSCLC).[1] The majority of patients with NSCLC have advanced stage (IIIB or IV) disease at the time of diagnosis and thus are not candidates for surgery. For these patients, systemic chemotherapy remains the standard treatment option, but its effects are limited and its severe adverse side effects significantly affect patient's quality of life.[2] The epidermal growth factor receptor (EGFR)-dependent pathway plays an important role in NSCLC proliferation; it is activated in more than half of patients with NSCLC.[3] Small-molecule EGFR-tyrosine kinase inhibitors (EGFR-TKIs) can block the EGFR-dependent pathway; their development provides a new treatment option and offers new hope for patients with advanced NSCLC. Certain NSCLC patient subgroups (ie, women, East Asians, never-smokers, and adenocarcinoma) more commonly exhibit EGFR-sensitive mutations (deletion of

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exon 19 and the L858R mutation in exon 21).[4,5] Patients with EGFR-mutant NSCLC are sensitive to EGFR-TKIs, such as gefitinib, erlotinib, and icotinib, with the response to EGFR-TKIs reaching 70%–80%. The median survival time has been reported to reach 20–30 months, with a significant improvement in patient quality of life for those receiving EGFR-TKIs compared to those on chemotherapy.[6,7] Thus, EGFR-TKIs have been recommended in the National Comprehensive Cancer Network guidelines as a first-line treatment option and are commonly used for patients with advanced NSCLC who harbor EGFR-sensitive mutations.

Despite its high remission and cure rates, TKI treatment will inevitably lead to acquired drug resistance.[8] Various resistance mechanisms have been reported. The acquired T790M mutation in exon 20 of EGFR is the most common mechanism of resistance to first-generation EGFR-TKI and is present in ~50%–60% of resistant cases.[9–11] Third-generation EGFR inhibitors, such as AZD9291 (osimertinib, mereletinib) and CO-1686 (rociletinib), have emerged as potential agents to block the growth of EGFR T790M-positive tumors.[12,13] Recently, in an effort to delay the development of drug resistance and improve the curative effect of EGFR-TKI as a first-line treatment, close attention has been paid to the combination of EGFR-TKI and chemotherapy as first-line treatment for EGFR-mutant advanced NSCLC. Given their different mechanisms of action, the combination of EGFR-TKI and chemotherapy may improve outcomes.[14] However, the results of several previous randomized controlled trials, including INTACT-1, INTACT-2, TRIBUTE, and TALENT, showed that the combination was no more beneficial than chemotherapy alone.[15–18] The possible reason for the failure to achieve positive results was not selecting patients harboring EGFR-sensitizing mutations. The studies carried out by Fred R evaluated the treatment outcomes with erlotinib alone or intercalating erlotinib and chemotherapy in advanced NSCLC patients who did not receive any prior or current anticancer therapy. The results showed that patients with activated EGFR mutations treated with erlotinib alone had better response rates, better progression-free survival (PFS), and better overall survival (OS) than those who received intercalating therapy.[19] The study of CALGB 30406 performed a similar comparison and suggested that improving the PFS of patients with EGFR-mutant NSCLC by adding chemotherapy to erlotinib is unlikely.[20] However, in the studies of B Han and Ying Cheng, the combination of gefitinib and chemotherapy improved PFS compared with gefitinib alone in patients with advanced NSCLC and activated EGFR mutations.[21,22] The efficacy of first-line treatment

with a combination of EGFR-TKI and chemotherapy in improving survival remains controversial.

Icotinib (Betta Pharmaceuticals Co., Ltd, Hangzhou, China), a first-generation EGFR-TKI, is an orally administered, reversible small-molecule EGFR-TKI, which has independent intellectual property rights in the People's Republic of China. Icotinib has shown equivalent curative effects, milder adverse reactions, better tolerability, and lower prices compared with gefitinib and erlotinib.[23] Its most common adverse events include rash and diarrhea, and no cases of interstitial lung disease have been reported. Icotinib is an important tool in the People's Republic of China for the first-line treatment of patients with advanced NSCLC who harbor sensitive EGFR mutations. In previous studies, most combination therapy focused on gefitinib or erlotinib, so the curative effect and safety of icotinib combined with chemotherapy remain unclear. To improve the effects of icotinib as the first-line treatment and to provide a clinical rationale for the use of a combination of EGFR-TKI and chemotherapy, we performed this retrospective analysis to comprehensively examine the overall efficacy and safety of icotinib in combination with chemotherapy as the first-line treatment of advanced NSCLC in patients harboring EGFR mutations in an uncontrolled real-life setting. In addition, several studies have reported that patients with advanced NSCLC and an EGFR exon19 deletion may have a longer PFS or OS following treatment with EGFR-TKI compared to patients with the L858R mutation.[24,25] Therefore, in our study, we also analyzed the curative effect of different treatments on different genetic mutations (EGFR exon 19 deletion or L858R mutation).

Patients and methods
Patients
Between January 2013 and December 2015, a total of 191 patients who met the inclusion criteria were eligible for our retrospective analysis. The patients' records were anonymized and de-identified prior to analysis. This study was approved by Chongqing Cancer Hospital Ethics Committee. Patients in our study have signed written informed consent.

The main inclusion criteria were 1) age ≥18 years; 2) Eastern Cooperative Oncology Group performance status (ECOG PS) ≤2; 3) pathologically diagnosed advanced NSCLC (stages IIIB or IV); 4) NSCLC harboring activated EGFR mutation (primarily exon 21 L858R point mutation or exon 19 deletion); 5) radiologically measurable or evaluable disease; 6) no other cancer; and 7) first-line treatment with received icotinib (125 mg tid)+chemotherapy or icotinib alone (125 mg tid) or chemotherapy alone. The main

exclusion criterion was if patients had received any prior or concurrent anticancer therapy for advanced NSCLC. Previous treatment during earlier-stage NSCLC was permitted.

Data collected from the medical records included age, sex, smoking history, EGFR mutation type, best response, toxicities, and survival data.

Assessment of efficacy and adverse events

The Response Evaluation Criteria in Solid Tumors was used to evaluate tumor response. The primary end point was PFS, which was defined as the period from the initial administration of icotinib or chemotherapy to tumor progression, death from any cause, or the last follow-up (calculated according to the event that occurred first). Secondary end points included OS, objective response rate (ORR), disease control rate (DCR), and toxicities. OS was defined as the span between the initiation of icotinib or chemotherapy and the date of death or the deadline of follow-up. ORR was defined as the rate of complete response (CR) and partial response (PR). DCR was defined as the rate of CR, PR, or stable disease. Adverse events were assessed according to Common Terminology Criteria for Adverse Events of the National Cancer Institute (version 3.0).

Statistical analysis

The chi-squared (χ^2) test was used for comparisons of ORR and DCR intergroups at a significance level of 5% (a=0.05, two-sided). The Kaplan–Meier method was utilized to obtain PFS and OS. The log-rank test was used to compare the significance between groups. The multivariate Cox regression model was used to calculate the hazard ratios. p-values of <0.05 ($p<0.05$) were considered statistically significant. SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

The overall curative effect and safety evaluation of different treatments

Patient characteristics

The study population included 92 men (48.2%) and 99 women (51.8%). The median age of the population was 60.8 years (range, 39–80 years). Of the 191 patients, 59 received icotinib+chemotherapy (group A), 75 received icotinib alone (group B), and 57 received chemotherapy alone (group C). The patients' baseline characteristics (age, sex, smoking history, ECOG PS, and EGFR mutation) are summarized in Table 1. The three groups were comparable with respect to disease and demographic characteristics. All patients had histologically proven adenocarcinoma of the lung. Most patients were nonsmokers with good ECOG PS (0–1). Approximately 53.4% of the patients (n=102) were found to have an EGFR exon 19 deletion, while 46.6% (n=89) had an EGFR exon 21 L858R point mutation in the EGFR gene. In group A, the chemotherapy regimens contained pemetrexed+cisplatin/carboplatin (n=20, 33.9%) and paclitaxel+cisplatin/carboplatin (n=39, 66.1%). In group C, the chemotherapy regimens contained pemetrexed+cisplatin/carboplatin (n=25, 43.9%) and paclitaxel+cisplatin/carboplatin (n=32, 56.1%).

Short-term curative effects

As shown in Table 2, the ORR was higher in group A than in group B (64.4% vs 46.7%, $p<0.05$). ORR in group B was

Table 1 Characteristics of all patients

Characteristics	I+C (group A, n=59)	I (group B, n=75)	C (group C, n=57)	Total (n=191)
Median age (years)	62.0	60.6	59.9	60.8
Sex				
Male	40.7% (n=24)	37.3% (n=28)	47.4% (n=27)	41.4% (n=79)
Female	59.3% (n=35)	62.7% (n=47)	52.6% (n=30)	58.6% (n=112)
Smoking history				
Nonsmoker	61.0% (n=36)	65.3% (n=49)	59.6% (n=34)	62.3% (n=119)
Smoker	39.0% (n=23)	34.7% (n=26)	40.4% (n=23)	37.7% (n=72)
ECOG performance status score				
0–1	100% (n=59)	96.0% (n=72)	98.2% (n=56)	97.9% (n=187)
2	0% (n=0)	4.0% (n=3)	1.8% (n=1)	2.1% (n=4)
Type of EGFR mutation				
Exon 19 deletion	52.5% (n=31)	56.0% (n=42)	50.9% (n=29)	53.4% (n=102)
L858R	47.5% (n=28)	44.0% (n=33)	49.1% (n=28)	46.6% (n=89)
Histologic diagnosis				
Adenocarcinoma	100%	100%	100%	100%

Abbreviations: C, chemotherapy; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; I, icotinib; I+C, icotinib+chemotherapy.

Table 2 Short-term curative effects of all patients

Curative effects	I+C (group A, n=59)	I (group B, n=75)	C (group C, n=57)
Best response			
CR	1.7% (n=1)	0% (n=0)	0% (n=0)
PR	62.7% (n=37)	46.7% (n=35)	26.3% (n=15)
SD	30.5% (n=18)	45.3% (n=34)	43.9% (n=25)
PD	5.1% (n=3)	8.0% (n=6)	29.8% (n=17)
ORR (%)	64.4	46.7	26.3
DCR (%)	94.9	92.0	70.2

Abbreviations: C, chemotherapy; CR, complete remission; DCR, disease control rate; I, icotinib; I+C, icotinib+chemotherapy; ORR, overall response rate; PD, progression disease; PR, partial disease; SD, stable disease.

better than that in group C (46.7% vs 26.3%, $p<0.05$). The DCRs in group A, group B, and group C were 94.9%, 92.0%, and 70.2%, respectively; there was no statistically significant difference between group A and group B ($p>0.05$), both of which were superior to group C ($p<0.05$).

Survival analysis

As of January 2017, 188 patients (98.4%) had reached the end point of disease progression or death. The median progression-free survival (mPFS) for the patients in group A, group B, and group C was 11.569 months (95% CI, 10.347–12.764), 8.607 months (95% CI, 7.806–9.407), and 6.544 months (95% CI, 5.634–7.453), respectively. The results suggest a favorable trend in PFS for the patients treated with icotinib+chemotherapy compared to those treated with icotinib alone ($p<0.001$, Figure 1A). In addition, patients treated with icotinib alone had significantly longer PFS compared to those who were treated with chemotherapy ($p<0.05$, Figure 1A). At the last follow-up, 38.7% (n=74) patients were still alive (24 patients in group A; 31 patients in group B; 19 patients in group C). The median

OS was 24.379 months (95% CI, 21.125–27.632) in group A, 20.244 months (95% CI, 18.493–21.995) in group B, and 20.633 months (95% CI, 18.148–23.117) in group C. While the OS data are immature, better OS was observed in group A compared to group B ($p<0.05$, Figure 1B). The OS comparison between group B and group C did not reach statistical significance ($p>0.05$, Figure 1B).

Adverse events

As shown in Table 3, The most common adverse events in group A were hematologic toxicities (neutropenia 50.8%; anemia 40.7%; thrombocytopenia 18.6%; leukopenia 22.0%), gastrointestinal reactions (nausea 39.0%; vomiting 39.0%; diarrhea 33.9%; constipation 11.9%), skin reactions (rash 52.5%), and liver function impairment (aspartate transaminase [AST]/alanine transaminase [ALT] elevation 37.3%). Other common adverse events included stomatitis (22.0%), fatigue (25.4%), and alopecia (16.9%). The most common adverse events in group B were rash (30.7%), diarrhea (21.3%), and AST/ALT elevation (12.0%). The most common adverse events in group C were hematologic toxicities (neutropenia 42.1%; anemia 50.9%; thrombocytopenia 22.8%; leukopenia 22.8%), gastrointestinal reaction (nausea 40.4%; vomiting 40.4%; diarrhea 21.0%; constipation 21.0%), skin reactions (rash 14.0%), and liver function impairment (AST/ALT elevation 24.6%). Other common adverse events included stomatitis (5.3%), fatigue (24.6%), and alopecia (22.8%). Hematologic adverse events and gastrointestinal reactions occurred with similar incidence in groups A and C, consistent with the toxicity profile of chemotherapy. Icotinib did not seem to exacerbate these toxicities. The adverse events related to icotinib were skin
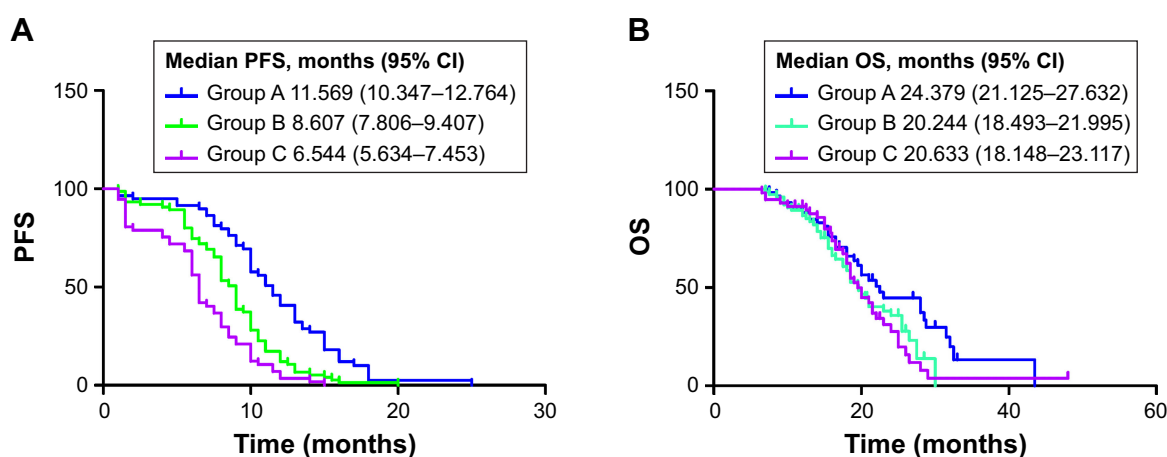

Figure 1 Kaplan–Meier curve of PFS (**A**) and OS (**B**) for all patients.
Notes: Group A, 59 patients received icotinib+chemotherapy; Group B, 75 patients received icotinib alone; Group C, 57 patients received chemotherapy alone.
Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 3 Adverse events

Toxicity	I+C (group A, n=59)		I (group B, n=75)		C (group C, n=57)	
	AE	Grade 3 or 4	AE	Grade 3 or 4	AE	Grade 3 or 4
Neutropenia	30 (50.8%)	8 (13.6%)	0 (0.0%)	0 (0.0%)	24 (42.1%)	4 (7.0%)
Anemia	24 (40.7%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	29 (50.9%)	5 (8.8%)
Thrombocytopenia	11 (18.6%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	13 (22.8%)	0 (0.0%)
Leucopenia	13 (22.0%)	0 (0.0%)	4 (5.3%)	0 (0.0%)	13 (22.8%)	3 (5.3%)
Rash	31 (52.5%)	5 (8.5%)	23 (30.7%)	5 (6.7%)	8 (14.0%)	0 (0.0%)
Stomatitis	13 (22.0%)	2 (3.4%)	7 (9.3%)	2 (2.7%)	3 (5.3%)	0 (0.0%)
Nausea	23 (39.0%)	2 (3.4%)	4 (5.3%)	0 (0.0%)	23 (40.4%)	4 (7.0%)
Vomiting	23 (39.0%)	0 (0.0%)	5 (6.7%)	0 (0.0%)	23 (40.4%)	2 (3.5%)
Diarrhea	20 (33.9%)	0 (0.0%)	16 (21.3%)	0 (0.0%)	12 (21.0%)	2 (3.5%)
Constipation	7 (11.9%)	0 (0.0%)	7 (9.3%)	0 (0.0%)	12 (21.0%)	0 (0.0%)
AST/ALT elevation	22 (37.3%)	5 (8.5%)	9 (12.0%)	0 (0.0%)	14 (24.6%)	2 (3.5%)
Fatigue	15 (25.4%)	0 (0.0%)	5 (6.7%)	0 (0.0%)	14 (24.6%)	0 (0.0%)
Alopecia	10 (16.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (22.8%)	0 (0.0%)
Pneumonitis	3 (5.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)	0 (0.0%)

Abbreviations: AE, adverse events; ALT, alanine transaminase; AST, aspartate transaminase; C, chemotherapy; I, icotinib; I+C, icotinib+chemotherapy.

and gastrointestinal events, most of which were mild. Grade 3 or 4 adverse events occurred more often with combination therapy and chemotherapy alone. No drug-related interstitial lung disease or drug-related death was observed.

The curative effect of different treatments on exon 19 deletion in the EGFR gene

Patient characteristics

A total of 102 patients had EGFR exon 19 deletion. Of these, 31 patients received icotinib+chemotherapy (group A1), 42 patients received icotinib alone (group B1), and 29 patients received chemotherapy alone (group C1). Patients' baseline characteristics (age, sex, smoking history, and ECOG PS) are summarized in Table 4.

Short-term curative effects

These results are shown in Table 5. The ORR in group A1 was higher than that in group B1 (74.2% vs 50%, $p<0.05$),

while the ORR in group B1 was superior to that in group C1 (50% vs 24.1%, $p<0.05$). The DCR difference between group A1 and group B1 did not reach statistical significance (96.8% vs 92.9%, $p>0.05$); the DCR in group B1 was better than that in group C1 (92.9% vs 69%, $p<0.05$).

Survival analysis

The mPFS for the patients in group A1, group B1, and group C1 was 13.391 months (95% CI, 11.636–15.146), 9.202 months (95% CI, 8.122–10.283), and 5.655 months (95% CI, 4.395–6.915), respectively. The patients treated with icotinib+chemotherapy had longer PFS compared to those treated with icotinib alone. In addition, patients treated with icotinib alone had significantly longer PFS compared to those treated with chemotherapy ($p<0.001$, Figure 2A). The median OS was 26.096 months (95% CI, 21.533–30.660) in group A1, 20.470 months (95% CI, 18.018–22.923) in group B1, and 20.618 months (95% CI, 16.987–24.248) in group C1. Better OS was observed in group A1 compared to

Table 4 Characteristics of patients with EGFR 19 exon deletion

Characteristics	I+C (group A1, n=31)	I (group B1, n=42)	C (group C1, n=29)	Total (n=102)
Median age (years)	62.1	61.7	59.7	61.2
Sex				
Male	35.5% (n=11)	38.1% (n=16)	37.9% (n=11)	37.3% (n=38)
Female	64.5% (n=20)	61.9% (n=26)	62.1% (n=18)	62.7% (n=64)
Smoking history (%)				
Nonsmoker	58.1% (n=18)	66.7% (n=28)	65.5% (n=19)	63.7% (n=65)
Smoker	41.9% (n=13)	33.3% (n=14)	34.5% (n=10)	36.3% (n=37)
ECOG performance status score				
0–1	100% (n=31)	95.2% (n=40)	100% (n=29)	93.2%
2	0% (n=0)	4.8% (n=2)	0% (n=0)	6.8%

Abbreviations: C, chemotherapy; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; I, icotinib; I+C, icotinib+chemotherapy.

Table 5 Short-term curative effects of patients with EGFR 19 exon deletion

Curative effects	I+C (group A1, n=31)	I (group B1, n=42)	C (group C1, n=29)
Best response			
CR	3.2% (n=1)	0% (n=0)	0% (n=0)
PR	71.0% (n=22)	50.0% (n=21)	24.1% (n=7)
SD	22.6% (n=7)	42.9% (n=18)	44.8% (n=13)
PD	3.2% (n=1)	7.1% (n=3)	31.0% (n=9)
ORR (%)	74.2	50.0	24.1
DCR (%)	96.8	92.9	69.0

Abbreviations: C, chemotherapy; CR, complete remission; DCR, disease control rate; EGFR, epidermal growth factor receptor; I, icotinib; I+C, icotinib+chemotherapy; ORR, overall response rate; PD, progression disease; PR, partial disease; SD, stable disease.

group B1 ($p<0.05$, Figure 2B). The OS comparison between group B and group C did not reach statistical significance ($p>0.05$, Figure 2B).

The curative effect of different treatments on patients with L858R mutation in the EGFR gene

Patient characteristics

A total of 89 patients harbored the L858R point mutation in the EGFR gene. Of these patients, 28 received icotinib+chemotherapy (group A2), 33 received icotinib alone (group B2), and 28 received chemotherapy alone (group C2). The patients' baseline characteristics (age, sex, smoking history, ECOG PS, and EGFR mutation) are summarized in Table 6.

Short-term curative effects

These results are shown in Table 7. No statistically significant difference was found in the ORR between group A2

and group B2 (53.6% vs 42.4%, $p>0.05$). While the ORR in group B2 was higher than that in group C2, there was no statistically significant difference between the two groups (42.4% vs 28.6%, $p>0.05$). The difference in DCR between group A2, group B2, and group C2 did not reach statistical significance (92.9% vs 90.9% vs 71.4%, $p>0.05$).

Survival analysis

The median PFS for the patients in group A2, group B2, and group C2 was 9.571 months (95% CI, 8.290–10.853), 7.848 months (95% CI, 6.692–9.005), and 7.464 months (95% CI, 6.219–8.709), respectively. The median OS was 21.587 months (95% CI, 18.251–24.922) in group A2, 19.822 months (95% CI, 17.343–22.302) in group B2, and 20.125 months (95% CI, 17.847–22.404) in group C2.

There was a favorable trend in PFS for the patients treated with icotinib+chemotherapy compared to those treated with icotinib alone ($p<0.05$, Figure 3A), while there was no difference between the PFS in group B2 and group C2 ($p>0.05$, Figure 3A). Although the OS in group A2 was ~3 months longer than that in group B2, there was no statistically significant difference between two groups ($p>0.05$, Figure 3B). The OS comparison between group B2 and group C2 did not reach statistical significance ($p>0.05$, Figure 3B).

Discussion

Based on large clinical trials, the first-line treatment of choice for advanced NSCLC harboring EGFR mutations is EGFR-TKI.[24] However, drug resistance seriously reduces the curative effect of TKI. Clinical trials of EGFR-TKI combined with chemotherapy compared to EGFR-TKI alone are becoming more popular in an effort to delay the development of resistance and improve distant disease control. However,
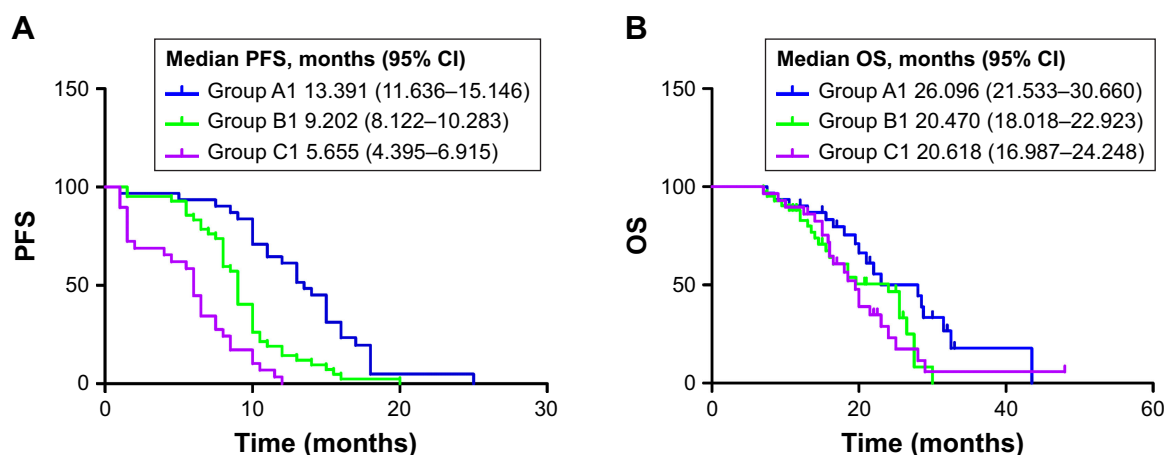

Figure 2 Kaplan–Meier curve of PFS (**A**) and OS (**B**) for patients with epidermal growth factor receptor exon 19 deletion.
Notes: Group A1, 31 patients received icotinib+chemotherapy; Group B1, 42 patients received icotinib alone; Group C1, 29 patients received chemotherapy alone.
Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 6 Characteristics of patients with EGFR L858R mutation

Characteristics	I+C (group A2, n=28)	I (group B2, n=33)	C (group C2, n=28)	Total (n=89)
Median age (years)	61.8	59.3	60.2	60.4
Sex				
Male	46.4% (n=13)	36.4% (n=12)	57.1% (n=16)	46.1% (n=41)
Female	53.6% (n=15)	63.6% (n=21)	42.9% (n=12)	53.9% (n=48)
Smoking history (%)				
Nonsmoker	64.3% (n=18)	63.6% (n=21)	53.6% (n=15)	60.7% (n=54)
Smoker	35.7% (n=10)	36.4% (n=12)	46.4% (n=13)	39.3% (n=35)
ECOG performance status score				
0–1	100% (n=28)	97.0% (n=32)	96.4% (n=27)	97.8%
2	0% (n=0)	3.0% (n=1)	3.6% (n=1)	2.2%

Abbreviations: C, chemotherapy; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; I, icotinib; I+C, icotinib+chemotherapy.

to date, no consensus has been reached regarding the efficacy of EGFR-TKI combined with chemotherapy in the first-line treatment of patients with NSCLC harboring EGFR mutations. We conducted this retrospective analysis to investigate the overall efficacy of icotinib with or without chemotherapy as first-line treatment for NSCLC patients with EGFR mutations. To our knowledge, ours is the first case–control study comparing the effectiveness of icotinib+chemotherapy and icotinib or chemotherapy alone in EGFR-mutant NSCLC patients.

A total of 191 patients were enrolled in our study; five matching variables (age, sex, smoking history, ECOG PS, and type of EGFR mutation) were selected. Statistically, it is complicated to adjust various types of chemotherapy and use periods for each chemotherapeutic agent. Therefore, the primary end point of this study was PFS rather than OS. For all patients, we found a statistically significant difference in PFS between the three groups, suggesting that the effectiveness of icotinib+chemotherapy was better than that of icotinib or chemotherapy alone and that the effectiveness of icotinib alone was better than that of chemotherapy alone. The results of our study also suggest that icotinib combined with chemotherapy as first-line treatment is associated with a better ORR in advanced NSCLC with EGFR mutations.

Although the OS data are immature, better OS was observed in the combination group compared with the icotinib alone or chemotherapy alone groups, while there was no significant difference between the patients treated with icotinib and chemotherapy, which may be associated with the follow-up treatment. Given the retrospective nature of this study, toxicity profiles were not always complete. We observed that adverse events were more frequent in the icotinib+chemotherapy and chemotherapy groups. Although some patients experienced a grade 3 or higher adverse event in the combination group, these events were predictable and manageable. No occurrence of an interstitial lung disease event was noted in this cohort. All of the drugs were well tolerated, and no treatment-related mortality was observed.

We also observed the curative effect of different treatments on patients harboring different EGFR mutations. The results showed that icotinib combined with chemotherapy significantly prolonged the PFS (~4 months) compared to icotinib or chemotherapy alone for the patients who had the EGFR exon 19 deletion. The combination treatment also significantly prolonged the OS (~6 months) in this group of patients. However, for the patients with the EGFR L858R mutation, although the combination of icotinib and chemotherapy extended the PFS, it did not significantly prolong

Table 7 Short-term curative effects of patients with EGFR L858R mutation

Curative effects	I+C (group A2, n=28)	I (group B2, n=33)	C (group C2, n=28)
Best response			
CR	0% (n=0)	0% (n=0)	0% (n=0)
PR	53.6% (n=15)	42.4% (n=14)	28.6% (n=8)
SD	39.3% (n=11)	48.5% (n=16)	42.8% (n=12)
PD	7.1% (n=2)	9.1% (n=3)	28.6% (n=8)
ORR (%)	53.6	42.4	28.6
DCR (%)	92.9	90.9	71.4

Abbreviations: C, chemotherapy; CR, complete remission; DCR, disease control rate; EGFR, epidermal growth factor receptor; I, icotinib; I+C, icotinib+chemotherapy; ORR, overall response rate; PD, progression disease; PR, partial disease; SD, stable disease.
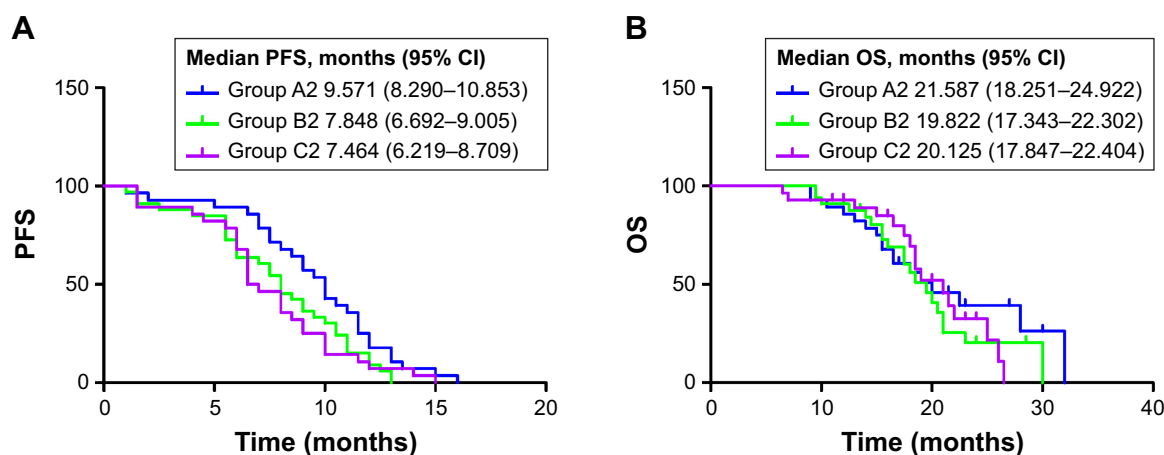
Figure 3 Kaplan–Meier curve of PFS (**A**) and OS (**B**) for patients with epidermal growth factor receptor exon 21 L858R mutation.
Notes: Group A2, 28 patients received icotinib+chemotherapy; Group B2, 33 patients received icotinib alone; Group C2, 28 patients received chemotherapy alone.
Abbreviations: OS, overall survival; PFS, progression-free survival.

the OS. Previous studies had found that advanced NSCLC patients harboring the EGFR exon 19 deletion may experience a better curative effect when treated with EGFR-TKI compared to the patients who had the L858R mutation. We also found that the patients who had EGFR exon 19 deletion can obtain more survival benefit when treated with icotinib combined with chemotherapy or icotinib alone compared to L858R-mutant patients.

This real-life analysis has several limitations including its small sample size, retrospective nature, and the heterogeneity of treatment regimens. Although five important baseline variables with baseline characteristics were matched between the three groups, the chemotherapy regimens and number of administered treatments varied and were not considered. The difference might have introduced potential bias, which may have affected the outcomes of the study. Furthermore, because of the small number of patients, the analysis is limited in its ability to provide better therapy. Moreover, due to the retrospective nature, other unmeasured confounding factors may have been introduced to the treatment groups. Nevertheless, the study data do reflect clinical practices at that time; we believe that this analysis provides valuable real-life evidence regarding treatments received and outcomes experienced by NSCLC patients with EGFR-sensitive mutations.

Conclusion

Our results are consistent with previous studies on erlotinib or gefitinib, highlighting that EGFR-mutated advanced NSCLC patients can experience better treatment effectiveness if they are treated with an icotinib/chemotherapy combination compared with icotinib or chemotherapy alone, especially for those harboring the EGFR exon 19 deletion. The modest increase in toxicity was clinically manageable. These results

suggest that patients with NSCLC with activating EGFR mutations may obtain a clinical benefit from the addition of chemotherapy to EGFR-TKIs. If the combination of chemotherapy plus EGFR-TKI is used as the first-line treatment, the third-generation EGFR-TKI can then be used after progression if patients are confirmed to have the T790M mutation.[12] Chemotherapy agents other than the first-line treatment may still be used after progression. The combination of chemotherapy and an EGFR-TKI may be a new treatment option for patients with EGFR mutation-positive NSCLC, which may improve clinical outcomes compared with the current standard of care. Because our study was based on clinical data from a small sample of patients and given the tendency toward longer PFS or OS in patients treated with the icotinib/chemotherapy combination, larger prospective trials should be conducted to determine the true efficacy and toxicity of these treatments. Indeed, a prospective study with a larger patient population is required to confirm our findings. In addition, the types of chemotherapeutic drugs that can achieve a better curative effect when combined with EGFR-TKI and the possible effects of EGFR-TKI combined with other agents, such as angiogenesis inhibitors or immunocheckpoint inhibitors, are promising avenues for future research.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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