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Geriatric Oncology

Epidermal Growth Factor Receptor (EGFR)-Tyrosine Kinase Inhibitor Treatment and Salvage Chemotherapy in EGFR-Mutated Elderly Pulmonary Adenocarcinoma Patients

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Adenocarcinoma • Elderly • Epidermal growth factor receptor • Tyrosine kinase inhibitors

ABSTRACT

Background. Lung cancer is frequently a disease of elderly patients. However, these patients are often treated less actively owing to a higher comorbidity rate and poor performance status. The efficacy of different treatments in elderly patients with epidermal growth factor receptor (*EGFR*)-mutated lung cancer is still unknown.

Materials and Methods. We retrospectively reviewed the records of our pulmonary adenocarcinoma patients treated between 2010 and 2013. Data on patient age, type of tumor *EGFR* mutation, response to first-line EGFR-tyrosine kinase inhibitor (TKI) treatment, type of salvage chemotherapy, and efficacy of EGFR-TKI and salvage chemotherapy were collected.

Results. In all, 473 of 1,230 stage IV adenocarcinoma patients had an *EGFR* mutation, and 330 of them received first-line TKI treatment. Of the 330 patients, 160 were ≥70 years old (elderly group) and 170 were <70 years old (younger group). The response rate and progression-free survival (PFS) with first-line TKI treatment were not significantly different. The elderly group had shorter median survival. A total of 107 patients received salvage chemotherapy after first-line EGFR-TKI treatment: 45 in the elderly group and 62 in the younger group. Their response rate and PFS were not significantly different; however, the younger group had longer median survival. Additional subgroup analysis showed that younger patients who received platinum-based chemotherapy or combination chemotherapy had better median survival than did the elderly patients. The PFS was longer among younger patients receiving a platinum-based regimen than that among the elderly patients.

Conclusion. Elderly patients with disease progression after first-line EGFR-TKI treatment can receive chemotherapy and have a response rate similar to that of younger patients.

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Implications for Practice: The aim of the present study was to investigate the efficacy of first-line epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment in elderly patients and the outcomes of subsequent salvage chemotherapy after disease progression. The most important finding was that elderly patients with disease progression after first-line EGFR-TKI treatment can receive salvage chemotherapy and have a response rate similar to that of younger patients who received salvage chemotherapy.

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide. Non-small-cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases [1]. Despite the advances in NSCLC treatment, such as third-generation chemotherapy, adjuvant chemotherapy, maintenance therapy, epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) therapy, and anaplastic lymphoma kinase-TKI therapy, the 5-year survival rate is only approximately 5%–20% [2–4].

Lung cancer is mostly a disease of the elderly. Previous studies have reported that the lung cancer incidence rate is higher in older individuals, with one third of these patients older than 70 years [2]. In addition, elderly patients with lung cancer are often treated less actively because of their comorbidities [5]. Kuo et al. reported that older patients frequently did not receive treatment that was as aggressive as that given to younger patients and had poorer outcomes [6]. Therefore, clinical studies

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of elderly lung cancer patients who are intent on improving their survival and/or quality of life are important.

After the Iressa Pan-Asia study and several similar prospective studies showed positive results with EGFR-TKI treatment, it was suggested that patients with tumor *EGFR*-mutated lung cancer should receive EGFR-TKI treatment instead of chemotherapy as their initial treatment [7]. EGFR-TKI treatment was also a good choice for elderly patients with *EGFR* mutations, because with this treatment, their quality of life improved, the progression-free survival (PFS) was longer, and life-threatening toxicities were fewer than with traditional chemotherapy. Erlotinib monotherapy was reported recently to be relatively well tolerated by elderly patients with advanced NSCLC [8, 9]. Chen et al. also reported that erlotinib was more effective than oral vinorelbine in elderly patients with an *EGFR* mutation [10]. Although many studies have focused on first-line EGFR-TKI treatment for elderly patients, the treatment efficacy of second-line salvage chemotherapy for elderly patients remains unknown.

Many studies have discussed which treatment should be the optimal first-line chemotherapy for elderly patients unselected for an *EGFR* mutation. For example, single-agent vinorelbine treatment showed better overall survival (OS) and quality of life than the best supportive care as first-line treatment of elderly patients; paclitaxel plus carboplatin treatment resulted in better survival than single-agent gemcitabine or vinorelbine treatment; and subgroup analysis of pemetrexed plus carboplatin treatment showed better efficacy than pemetrexed treatment alone [11, 12]. A phase III study of NSCLC patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 (74 of the 205 study patients [36.1%] were 70 years old or older) also showed pemetrexed plus carboplatin had better efficacy than pemetrexed alone [13]. Also, a subgroup analysis compared the efficacy and toxicity of second-line chemotherapy in elderly NSCLC patients previously treated with chemotherapy [14]. The controversy over which chemotherapy regimen or agent to use has now been extended to elderly patients with acquired resistance after first line EGFR-TKI treatment. The aim of the present study was to investigate the efficacy of first-line EGFR-TKI treatment in elderly patients and the outcomes of subsequent salvage chemotherapy after disease progression.

Materials and Methods

Study Design and Patients

We retrospectively reviewed the medical records and imaging files of lung cancer patients diagnosed and treated between 2010 and 2013 in our hospital. We enrolled those patients who had stage IV adenocarcinoma (American Joint Committee on Cancer staging system, 7th edition) and a documented tumor *EGFR* mutation who had received first-line EGFR-TKI therapy in our hospital. Patients who stopped first-line EGFR-TKI treatment because of side effects and those still taking an EGFR-TKI without disease progression were included in the EGFR-TKI efficacy analysis but were excluded from the salvage chemotherapy analysis (Fig. 1). We also recorded the treatment strategies used after first-line EGFR-TKI therapy, including chemotherapy and the regimens used, radiotherapy alone, and supportive care alone. Patients who died, were lost to follow-up, who asked to continue or change to another targeted therapy, or who asked to stop salvage chemotherapy were all recorded. Among the patients who received second-line salvage chemotherapy, we excluded those who continued first-line EGFR-TKI, those lost to follow-up, those who stopped because of side effects, and those who had just started chemotherapy. The patients were divided into two groups according to age. One group included patients 70 years old or older (older group) and one included patients younger than 70 years old (younger group). To evaluate the effects of salvage chemotherapy after first-line EGFR-TKI treatment in these two groups, we retrospectively reviewed the cohorts from different perspectives. The institutional ethical review board of Taipei Veterans General Hospital approved the study (VGHIRB No. 2014-05-008AC). The clinical data, including age, gender, ECOG PS, smoking history, type of mutation, first-line EGFR-TKI used, regimens of salvage chemotherapy, treatment cycles, time of disease progression, and OS were recorded.

Efficacy Evaluation

A chest computed tomography scan (including the liver and adrenal glands) was performed within 3 weeks before starting the targeted therapy and chemotherapy and every 2 to 3 months thereafter or when confirmation of the treatment response or disease progression was required. The type of treatment response was accessed from the chest computed tomography scan using the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) [15]. PFS with targeted therapy and chemotherapy was defined as the duration from the date of initiating the targeted therapy or chemotherapy to the earliest sign of disease progression, as determined using the RECIST or death from any cause. If disease progression had not occurred at the last follow-up visit, PFS was considered to have been censored at that time. OS was defined as the period from the beginning of targeted therapy or chemotherapy to the date of death. OS was censored when the patients were still alive at the last follow-up visit.

EGFR Mutation Analysis

Tumor *EGFR* mutations were examined using one of two methods. Before the end of 2010, Sanger DNA sequencing was used. All the sequence variations were confirmed by multiple, independent polymerase chain reaction amplifications and repeated sequencing reactions. Beginning in 2011, most specimens were tested using the Scorpion amplification refractory mutation system method.

Statistical Analysis

All categorical variables were analyzed using chi-square tests. Two-sided *t* tests were used for continuous variables when comparing two groups. The targeted therapy and chemotherapy response rates were compared between the two groups. The median PFS and OS were calculated using the Kaplan-Meier method and compared using the log-rank test. Cox regression analysis was used for multivariate PFS and OS analysis. All statistical analyses were performed using SPSS software, version 19.0 (IBM Corp., Armonk, NY, http://www-01.ibm.com/software/analytics/spss/).

Results

Patients

Between 2010 and 2013, 1,230 patients in our hospital had stage IV adenocarcinoma. The results of tumor *EGFR* analysis were available for 872 patients. The 473 patients with *EGFR* mutations had classic mutations (exon 19 deletion and L858R)

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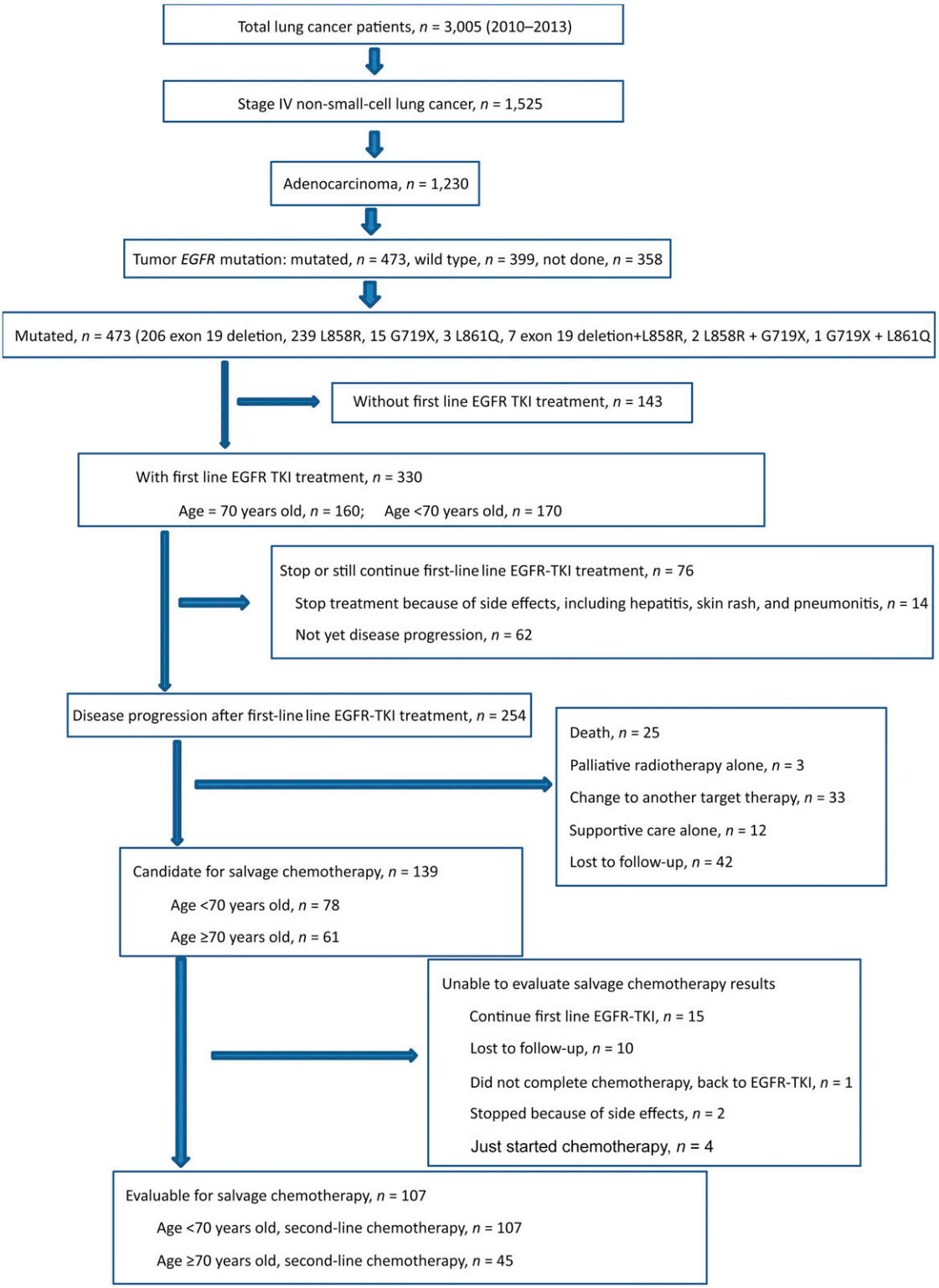

Figure 1. CONSORT diagram for the present study.
Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

and atypical mutations (G719X, L861Q). Of the 473 patients, 330 received first-line EGFR-TKI treatment. Of these patients, 160 were ≥70 years old (older group) and 170 were <70 years old (younger group). Of the 330 patients, 254 experienced disease progression; 139 patients received salvage chemotherapy, of whom, 107 were eligible for chemotherapy efficacy evaluations. Of these 107 patients, 45 were in the older group and 62 in the younger group (Fig. 1).

First-Line EGFR-TKI Treatment

Of the 330 patients who received first-line EGFR-TKI treatment, those in the younger group ($p = .001$) had a better

Table 1. First-line epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor response in 330 *EGFR*-mutated patients

Variable	Age ≥70 yr ($n = 160$)	Age <70 yr ($n = 170$)	p value
TKI			.245
Gefitinib	151 (94.4)	154 (90.6)	
Erlotinib	9 (5.6)	14 (8.2)	
Afatinib	0 (0)	2 (1.2)	
Gender, male	71 (44.4)	64 (37.6)	.220
Mutation			.904
Exon 19 deletion	63 (39.4)	71 (41.8)	
L858R	74 (46.3)	75 (44.1)	
Atypical	23 (14.4)	24 (14.1)	
Performance status			.001
0	16 (10.0)	41 (24.1)	
1	95 (59.4)	105 (61.8)	
2	40 (25.0)	19 (11.2)	
3	7 (4.4)	4 (2.4)	
4	2 (1.3)	1 (0.6)	
Smoking, yes	42 (26.3)	41 (24.3)	.705
Response rate			.209
Response	106 (72.6)	128 (80.0)	
Stable disease	22 (15.1)	15 (9.4)	
Progressive disease	18 (12.3)	17 (10.6)	
First-line TKI			
Complete treatment[a]	130 (81.8)	142 (84.5)	.555
Second-line chemotherapy	61 (38.1)	78 (45.9)	.154
Death	15 (9.4)	10 (5.9)	.231
Lost to follow-up	25 (15.6)	18 (10.6)	.174
Stopped because of side effects	5 (3.1)	9 (5.3)	.329
Median progression-free survival (mo)	11.267	10.867	.416
95% CI	8.597–13.936	9.054–12.679	
Median survival (mo)	21.300	26.467	.014
95% CI	18.162–24.438	23.297–29.636	
One-year survival	74 (70.5)	72 (73.5)	.635

Data presented as *n* (%), unless otherwise noted.
[a]Received TKI for more than 3 months.
Abbreviations: CI, confidence interval; TKI, tyrosine kinase inhibitor.

performance status. However, no difference in gender, smoking prevalence, or *EGFR* mutation type was noted between the 2 age groups (Table 1). The response rate for the older patients was 72.6% and was 80.0% for the younger patients ($p = .209$). Among the patients who received first-line EGFR-TKIs, the rate of completing treatment (defined as receiving first-line EGFR-TKIs for more than 3 months) was not significantly different (81.8% vs. 84.5%; $p = .555$). The mortality rate during EGFR-TKI treatment or before salvage therapy did not differ between the 2 groups (9.4% vs. 5.9%; $p = .231$). In addition, 15.6% of the older patients and 10.6% of the younger patients were lost to follow-up ($p = .174$). Our results also showed that 3.1% of the older patients and 5.3% of the younger patients stopped treatment because side effects from the EGFR-TKI ($p = .329$). Approximately 38.1% of the older patients and 45.9% of the younger patients who had received EGFR-TKI treatment could receive second-line salvage therapy after their disease had progressed.

No difference was seen in the sites of disease progression between the older and younger patients ($p = .736$). Also, no significant difference was found in PFS between the 2 age groups (median PFS 11.3 months in the older group vs. 10.9 months in the younger group; $p = .416$; Fig. 2A). The median survival was significantly longer for the younger patients than for the older patients (median survival, 26.5 vs. 21.3 months; $p = .014$; Fig. 3A). The 1-year survival rate was 70.5% for the older patients and 73.5% for the younger patients ($p = .635$; Table 1).

Second-Line Salvage Chemotherapy

A total of 45 older patients and 62 younger patients received second-line salvage chemotherapy (Table 2). No differences were found in gender, smoking habit, or performance status between these two groups of patients. The tumor response rate was 24.4% for the older patients and 30.6% for the younger patients. No significant difference was seen in PFS between the older and younger groups of patients (3.5 vs. 5.1 months; $p = .156$; Fig. 2B). However, the OS was longer for the younger patients than for the older patients (18.2 vs. 10.9 months; $p = .002$; Fig. 3B).

Platinum-Based Chemotherapy

A total of 30 older patients and 57 younger patients received platinum-based therapy (Table 3). No differences in gender, smoking habits, or performance status were noted between the 2 age groups. The tumor response rate in the older patients was 20.0% and was 31.6% in the younger patients ($p = .426$). Younger patients had a significantly higher treatment completion rate (96.5% vs. 80.0%; $p = .018$). PFS was significantly longer for the younger patients than for the older patients (5.1 vs. 3.2 months; $p = .033$; Fig. 2E). Also, the younger patients had significantly longer OS than did the older patients (18.8 vs. 11.1 months; $p = .004$; Fig. 3E).

Combination Chemotherapy

A total of 32 older patients and 58 younger patients received combination chemotherapy (Table 4). No differences in gender, smoking habits, or performance status were noted among the patients. The treatment response rate was not different between the 2 age groups (21.9% in the older group vs. 31.0% in the younger group; $p = .616$). The younger patients had a higher rate of treatment completion than did the older patients (94.8% vs. 81.3%; $p = .040$; Table 4). The PFS was insignificantly longer for the younger patients than for the older patients (4.9 vs. 3.9 months; $p = .474$; Fig. 2D), and the OS was longer in the younger group than in the older group (18.8 vs. 11.1 months; $p = .003$; Fig. 3D).

Pemetrexed-Based Chemotherapy

A total of 26 older patients and 54 younger patients received pemetrexed-based chemotherapy, including 51 with pemetrexed plus cisplatin, 19 with pemetrexed plus carboplatin, 6

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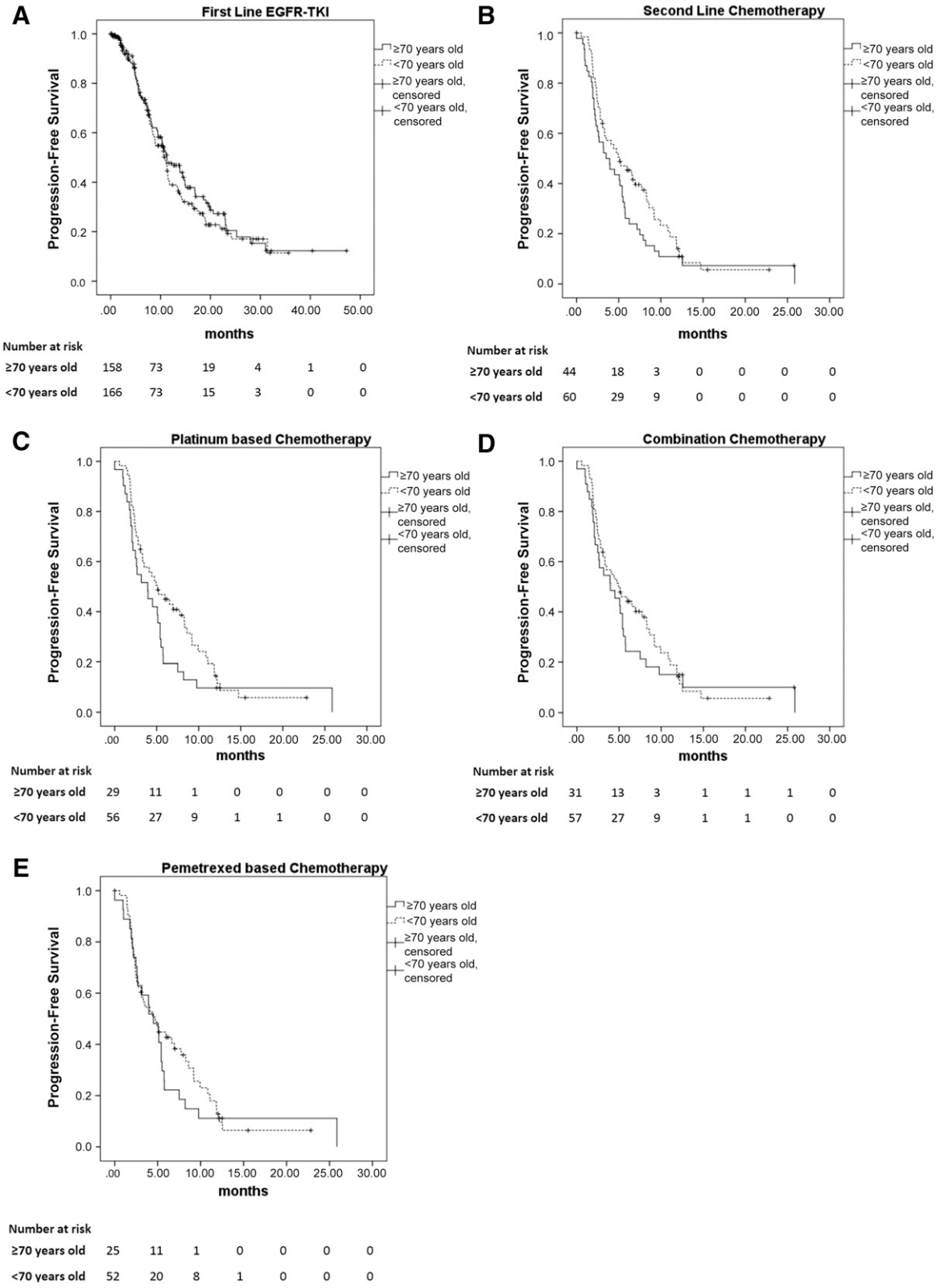

Figure 2. Progression-free survival (PFS) of patients who received first-line EGFR-TKI and salvage chemotherapy after failure of first-line EGFR-TKI treatment. **(A):** A total of 330 patients received first-line EGFR-TKI therapy. No significant difference was seen in PFS between the two age groups (median PFS, 11.3 months in the older group and 10.9 months in the younger group; $p = .416$). **(B):** No significant difference was found in PFS between the older and younger patients receiving second-line salvage chemotherapy (3.5 vs. 5.1 months; $p = .156$). **(C):** PFS was significantly longer for the younger patients than for the older patients receiving platinum-based chemotherapy (5.1 vs. 3.2 months; $p = .033$). **(D):** No significant difference was seen in PFS between the two age groups that received combination therapy (4.9 vs. 3.9 months; $p = .474$). **(E):** No significant difference was seen in PFS between the 2 age groups that received pemetrexed-based therapy (4.0 vs. 4.7 months; $p = .233$).

Abbreviation: EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

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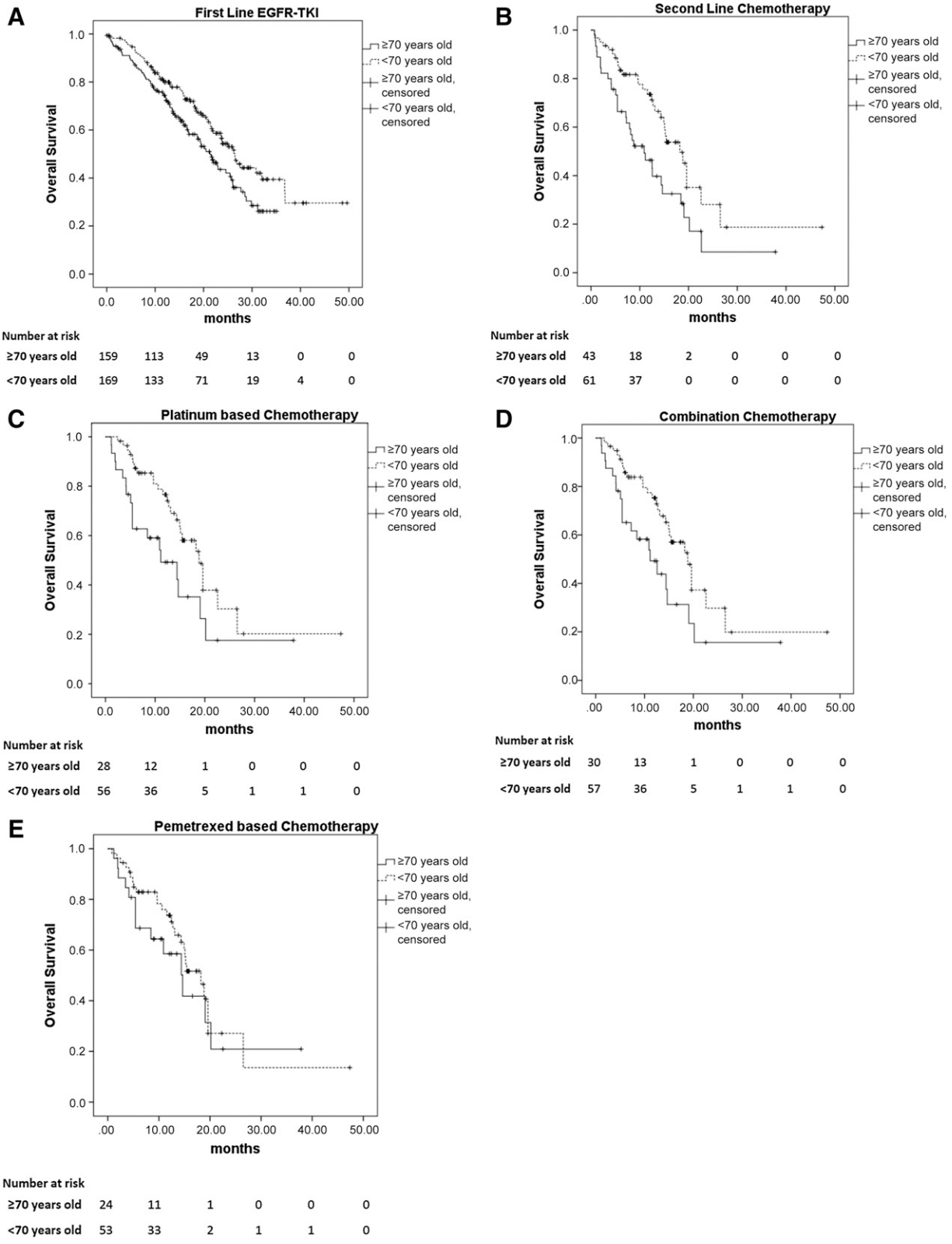

Figure 3. The median survival of patients who received first-line EGFR-TKI therapy and salvage chemotherapy after failure of first-line EGFR-TKI treatment. **(A):** A total of 330 patients received first-line EGFR-TKI therapy. The median survival was significantly longer for the younger patients than for the older patients (median survival, 26.5 vs. 21.3 months; $p = .014$). **(B):** The median survival was longer for the younger patients than for the older patients receiving second-line salvage chemotherapy (18.2 vs. 10.9 months; $p = .002$). **(C):** The overall survival (OS) was longer in the younger group than in the older group with platinum-based chemotherapy (18.8 vs. 11.1 months; $p = .004$). **(D):** The OS was longer in the younger group than in the older group when receiving combination therapy (18.8 vs. 11.1 months; $p = .003$). **(E):** No significant difference was found in the median survival between the 2 age groups that received pemetrexed-based therapy (14.4 vs. 18.2 months; $p = .162$).

Abbreviation: EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

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Table 2. Second-line chemotherapy status of patients with disease progression after first-line epidermal growth factor receptor-tyrosine kinase inhibitor treatment

Variable	Age ≥70 ($n = 45$)	Age <70 ($n = 62$)	p value
Gender, male	15 (33.3)	27 (43.5)	.285
Smoking, yes	11 (24.4)	19 (30.6)	.481
Performance status			.141
0	6 (13.3)	16 (25.8)	
1	29 (64.4)	39 (62.9)	
2	10 (22.2)	6 (9.7)	
3	0 (0)	1 (1.6)	
Response rate			.768
Response	11 (24.4)	19 (30.6)	
Stable disease	12 (26.7)	16 (25.8)	
Progressive disease	22 (48.9)	27 (43.5)	
Received 3 and more than 3 cycles	37 (82.2)	57 (91.9)	.129
Median progression-free survival (mo)	3.5	5.133	.070
95% CI	1.791–5.209	2.596–7.671	
Median survival (mo)	10.900	18.233	.002
95% CI	6.212–15.588	15.047–21.420	

Data presented as *n* (%), unless otherwise noted.
Abbreviation: CI, confidence interval.

Table 3. Patients who received second-line chemotherapy with a platinum-based regimen according to age

Variable	Age ≥70 ($n = 30$)	Age <70 ($n = 57$)	p value
Gender, male	10 (33.3)	24 (42.1)	.425
Performance status			.539
0	4 (13.3)	14 (24.6)	
1	22 (73.3)	36 (63.2)	
2	4 (13.3)	6 (10.5)	
3	0 (0)	1 (1.8)	
Smoking, yes	8 (26.7)	17 (29.8)	.757
TKI response			.409
Response	25 (86.2)	45 (78.9)	
Stable disease	3 (10.3)	5 (8.8)	
Progressive disease	1 (3.4)	7 (12.3)	
Chemotherapy response			
Response	6 (20.0)	18 (31.6)	.426
Stable disease	8 (26.7)	16 (28.1)	
Progressive disease	16 (53.3)	23 (40.4)	
Complete treatment	24 (80.0)	55 (96.5)	.018
Median progression-free survival (mo)	3.167	5.133	.033
95% CI	1.333–5.001	2.908–7.359	
Median survival (mo)	11.133	18.833	.004
95% CI	4.646–17.621	15.264–22.403	

Data presented as *n* (%), unless otherwise noted.
Abbreviations: CI, confidence interval; TKI, tyrosine kinase inhibitor.

Table 4. Patients who received second-line chemotherapy with a combination regimen according to age

Variable	Age ≥70 ($n = 32$)	Age <70 ($n = 58$)	p value
Gender, male	11 (34.4)	25 (43.1)	.418
Performance status			.381
0	4 (12.5)	15 (25.9)	
1	23 (71.9)	36 (62.1)	
2	5 (15.6)	6 (10.3)	
3	0 (0)	1 (1.7)	
Smoking, yes	8 (25.0)	17 (29.3)	.662
TKI response			.702
Response	26 (83.9)	46 (79.3)	
Stable disease	3 (9.7)	5 (8.6)	
Progressive disease	2 (6.5)	7 (12.1)	
Chemotherapy response			
Response	7 (21.9)	18 (31.0)	.616
Stable disease	9 (28.1)	16 (27.6)	
Progressive disease	16 (50.0)	24 (41.4)	
Complete treatment	26 (81.3)	55 (94.8)	.040
Median progression-free survival (mo)	3.933	4.933	.251
95% CI	1.392–6.474	2.387–7.480	
Median survival (mo)	11.133	18.833	.003
95% CI	6.014–16.252	15.248–22.419	

Data presented as *n* (%), unless otherwise noted.
Abbreviations: CI, confidence interval; TKI, tyrosine kinase inhibitor.

with pemetrexed, cisplatin, and bevacizumab, 2 with pemetrexed, carboplatin, and bevacizumab, and 2 with pemetrexed alone. No differences in gender, smoking habits, or performance status were noted between the 2 age groups. The tumor response rate with pemetrexed-based therapy was 23.1% for the older patients and 29.6% for the younger patients ($p = .751$). No significant difference was seen in PFS between the 2 age groups that received pemetrexed-based therapy (4.0 vs. 4.7 months; $p = .233$; Fig. 2C). Also, no difference was seen in OS (14.4 vs. 18.2 months; $p = .162$; Fig. 3C).

Multivariate Survival Analysis of Patients Who Received Salvage Chemotherapy

The Cox regression analysis test, including age, performance status, receipt of pemetrexed treatment, single-agent or combination chemotherapy, platinum-based or non-platinum-based treatment, response to previous EGFR-TKI treatment, and response to chemotherapy, was used for the multivariate PFS and OS analysis. The PFS and OS of the younger patients was significantly longer than that of the older patients ($p = .005$ and $p = .002$, respectively). In addition, those with a response to chemotherapy had statistically significantly longer PFS ($p = .015$) but not OS ($p = .227$).

Discussion

In 2007, Jackman et al. [8] treated patients unselected by mutation status who were >70 years old with erlotinib. The

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reported median PFS was 3.5 months, and the median OS was 10.9 months [8]. In 2008, Crinò et al. enrolled chemotherapy-naïve patients who were >70 years old and divided them into 2 groups. One of the groups received gefitinib and the other vinorelbine. The median PFS of the gefitinib group was 2.7 months and the OS was 5.9 months [9]. Few studies have compared the efficacy of EGFR-TKI treatment and chemotherapy in *EGFR*-mutated elderly and younger patients. Our data showed that when receiving active treatment that included EGFR-TKI and subsequent salvage chemotherapy, the PFS did not differ significantly between the younger and older patients (10.9 vs. 11.3 months, $p = .416$, and 5.1 vs. 3.5 months, $p = .070$, respectively, for EGFR-TKI and subsequent salvage chemotherapy). However, the OS of the younger patients was significantly longer than that of the older group (26.5 vs. 21.3 months, $p = .021$; and 18.2 vs. 10.9 months, $p = .014$, respectively, for EGFR-TKI and subsequent salvage chemotherapy).

A previous study suggested that advanced age alone should not preclude the use of chemotherapy. Although elderly patients needed more frequent hospital visits and were more likely to experience cancer symptoms and a deteriorated quality of life, they had similar survival rates [5]. Our data showed that more elderly patients than younger patients died and were lost to follow-up during EGFR-TKI treatment (9.4% vs. 5.9%, $p = .231$; and 15.6% vs. 10.6%, $p = .174$, respectively). However, elderly patients could tolerate and complete EGFR-TKI treatment as well as the younger patients did (3.1% vs. 5.3%, $p = .329$; and 81.8% vs. 84.5%, $p = .555$, respectively). In addition, our data showed that elderly patients who received second-line salvage chemotherapy after acquired resistance to first-line EGFR-TKI had a median OS of approximately 10.9 months. This is longer than the OS of patients who received the best supportive care in the previous study [11].

Treatment of acquired resistance to EGFR-TKI treatment in *EGFR*-mutated advanced NSCLC includes continuing EGFR-TKI, local ablation to oligoprogressive disease followed by reinitiation of TKI, combined targeted therapies such as afatinib and cetuximab, chemotherapy, or third-generation EGFR-TKI treatment [16]. Of these, third-generation EGFR-TKIs have been newly launched with promising efficacy in patients with an acquired T790M mutation [17, 18]. Up to now, chemotherapy was most often used as a salvage modality. However, the question remains of which chemotherapy agents to choose after elderly patients acquire resistance to EGFR-TKI. Goldberg et al. compared chemotherapy plus erlotinib with chemotherapy alone in advanced NSCLC patients who had received first-line EGFR-TKI and had acquired resistance. An improved response rate (63% vs. 21%; $p = .02$) was seen, but no significant difference was found in PFS (4.4 vs. 4.2 months; $p = .5$) or OS (14.2 vs. 15.0 months; $p = .37$) [19]. Another study showed that platinum-based combination regimens might be associated with better OS than other chemotherapy regimens or erlotinib as second-line chemotherapy after first-line gefitinib treatment, although the study did not focus on *EGFR*-mutated patients [20]. Our study results revealed a similar chemotherapy response rate for older and younger patients (24.4% vs. 30.6%; $p = .768$) and similar PFS (3.5 vs. 5.1 months; $p = .070$). The OS was longer for the younger patients than for the older patients (18.2 vs. 10.9 months; $p = .002$).

Although some studies have suggested that chemotherapy should be the first choice for patients with acquired EGFR-TKI resistance, no study has specifically reported on the treatment used for elderly patients [21, 22]. Ours is the first retrospective study to review the different chemotherapy regimens given after acquired resistance to first-line EGFR-TKI treatment in elderly patients and to compare the effects with those in younger patients. The response rate of the elderly in our study was 23.1% for pemetrexed-based chemotherapy, 21.9% for combination chemotherapy, and 20.0% for platinum-based chemotherapy, similar to the results from previous studies that focused on chemotherapy for an *EGFR*-mutated population not limited to the elderly [23, 24]. In our study, the PFS was not significantly different between the older and younger patients undergoing pemetrexed-based chemotherapy and combination chemotherapy but was longer in younger patients receiving platinum-based chemotherapy than that in the older patients (5.1 vs. 3.2 months; $p = .033$). The OS was better for the younger than for the older patients when using combination therapy and platinum-based chemotherapy.

Some limitations in our study should be mentioned. First, ours was a retrospective study; thus, undoubtedly, some selection bias was present. Owing to differences in patient characteristics, physicians might choose different chemotherapy regimens, which could confound the outcomes of the study. Second, we did not routinely perform repeat biopsy for patients who developed acquired resistance to first-line EGFR-TKI therapy. Histological changes could have occurred and influenced the treatment outcome. Finally, the population in our study was relatively small. A large, prospective, randomized trial is necessary to achieve definite answers to the questions raised. However, the issues of platinum versus nonplatinum, single versus combination chemotherapy, and pemetrexed versus nonpemetrexed use in first-line NSCLC treatment for elderly patients were not definitively answered, not to mention the issues surrounding *EGFR*-mutated elderly patients after they have developed acquired resistance to EGFR-TKI.

Conclusion

Elderly patients who have disease progression after first-line EGFR-TKI treatment can receive chemotherapy and have a chemotherapy response rate similar to that of younger patients.

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Disclosures

The authors indicated no financial relationships.

CME

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