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Review Article

First-line Treatment in Elderly Patients with Advanced Non-small Cell Lung Cancer

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Abstract

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer death worldwide, and more than 40% of patients are 70 years or older at the time of diagnosis. Based on the results of previous large-scale randomized phase III trials of elderly patients with advanced NSCLC, several single-agent chemotherapy regimens have been recommended as first-line treatment.

Recently, a large-scale clinical trial of targeted tyrosine kinase inhibitors for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) significantly prolonged survival and resulted in high response rates compared with standard chemotherapy as first-line treatment in patients with advanced NSCLC harboring *EGFR* mutations or the ALK fusion gene.

Although various first-line treatment options are currently available for patients with advanced NSCLC, it is unclear whether any of these treatments are advantageous in the first-line treatment of elderly patients. This review focuses on chemotherapy regimens and targeted agents, especially for EGFR, ALK, and vascular endothelial growth factor, based on the latest clinical data.

Keywords: Chemotherapy; Elderly patients; First-line therapy; Non-small cell lung cancer; Targeted therapy

Abbreviations

NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; EML4-ALK: echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; VEGF: vascular endothelial growth factor; RR: response rate; PFS: progression-free survival; QOL: quality of life; HR: hazard ratio; CI: confidence interval; PS: performance status; OS: overall survival; OR: odds ratio; AUC: area under the concentration-time curve; HR: hazard ration; HER: human epidermal receptor

Introduction

Lung cancer is most frequently diagnosed in people aged 65–74 years, with the median age at diagnosis being 70 years based on the Surveillance, Epidemiology, and End Results Program (http://seer.cancer.gov/), and mortality rates from this disease have increased among patients aged 70 years or older [1-2]. Many elderly patients with non-small cell lung cancer (NSCLC) have comorbidities and decreases in bone marrow capability, renal function, and drug clearance, which could negatively affect the severity of treatment-related toxicity. Although many clinical trials of patients with advanced NSCLC have been conducted, elderly patients aged 65 years or older accounted for only one-quarter of all participants, and only a few large-scale clinical trials of elderly patients with NSCLC have been designed [3-4].

In recent years, front-line molecular targeted therapies targeting specific oncogenes such as epidermal growth factor receptor (*EGFR*) mutations and the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene have greatly influenced survival and response in patients with advanced NSCLC harboring these specific oncogenes. An anti-growth factor vascular endothelial growth factor (VEGF) monoclonal antibody inhibitor combined with chemotherapy produced a higher response rate (RR) and longer progression-free survival (PFS) than standard chemotherapy for non-squamous cell NSCLC.

Currently, various therapies are offered as first-line treatments in elderly patients with advanced NSCLC. Here, we reviewed the front-line treatment strategy in elderly patients with advanced NSCLC with a focus on systemic chemotherapy and molecular targeted therapies.

Single-agent chemotherapy and non-platinum–doublet chemotherapy in non-selected elderly patients with advanced NSCLC

Among previous several phase III trials of non-platinum agents in elderly patients aged 70 years or older with advanced NSCLC; the ELVIS trial revealed that vinorelbine improved survival and quality of life (QOL) in patients compared to best supportive care [5]. Chemotherapy with vinorelbine significantly prolonged survival in the treatment group compared to the control group (6.9 months vs. 4.9 months, hazard ratio [HR] = 0.65, 95% confidence interval [CI] = 0.45–0.93, p = 0.03). Table 1 presents previous phase III trials of single-agent or combination chemotherapy using third-generation cytotoxic agents including gemcitabine, vinorelbine, and docetaxel in patients with advanced NSCLC [5-8]. Although combination chemotherapy with third-generation cytotoxic agents including gemcitabine and vinorelbine produced a higher RR than a single third-generation agent, no significant survival advantage was noted between combination and single-agent chemotherapy regimens excluding the trial conducted by Frasci el al. additionally, higher rates of toxicity were observed for the gemcitabine plus vinorelbine regimen

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Table 1: Phase III trials of third-generation cytotoxic agents as first-line treatment in patients with advanced NSCLC.

Study	PS	Number of patients	Age (years)	Treatment	RR (%)	Median OS	
ELVIS [5]	0–2	161	Median 74	VNR	19.7	6.9 mo	HR = 0.65 (95% CI = 0.45–0.93) $p = 0.03$
			Median 74	BSC	0	4.9 mo	
Frasci et al. [6]	0–2	120	Median 75	GEM+VNR	22	29 wk	HR = 0.48 (95% CI = 0.29–0.79) $p < 0.01$
			Median 74	VNR	15	18 wk	
MILES [7]	0–2	698	Median 74	GEM+VNR	21	7.0 mo	GEM+VNR vs. GEM $p = 0.65$ GEM+VNR vs. VNR $p = 0.93$
			Median 74	GEM	16	6.9 mo	
			Median 74	VNR	18	8.4 mo	
Kudoh et al. [8]	0–2	182	Median 76	DOC	22.7	14.3	HR = 0.78 (95% CI = 0.56–1.085) $p = 0.138$
			Median 76	VNR	9.9	9.9	

Abbreviations: NSCLC: Non-small Cell Lung Cancer; PS: Performance Status; RR: Response Rate; OS: Overall Survival; HR: Hazard Ratio; CI: Confidence Interval; VNR: Vinorelbine; BSC: Best Supportive Care; GEM: Gemcitabine; DOC: Docetaxel

than for the single-agent regimens. A subset analysis of some phase III trials comparing doublet chemotherapy with third-generation cytotoxic agent monotherapy for advanced NSCLC reported a higher RR and longer PFS in patients treated with doublet chemotherapy [9-10]. However, no significant difference was noted in survival between double and single-agent chemotherapy. Elderly patients aged 70 years or older and patients with a performance status (PS) of 2 were eligible for inclusion in these trials (Table 1). The RRs and overall survival (OS) times were 23–32% and 5.5–9.7 months, respectively, for gemcitabine-based combination chemotherapy including paclitaxel, vinorelbine, and docetaxel, compared to 13–18% and 5.1–6.4 months, respectively, for third-generation single-agent chemotherapy. Russo et al. reported in their literature-based meta-analysis of non-platinum chemotherapy for elderly patients with advanced NSCLC that although gemcitabine-based doublet chemotherapy was advantageous regarding RR, no survival benefit was noted between gemcitabine-based doublet chemotherapy and monotherapy with third-generation agents such as vinorelbine, docetaxel, and paclitaxel [11]. Based on their analysis of the data of four eligible phase III trials including a total of 1436 elderly patients with NSCLC, a statistically significant increase in the overall RR favoring doublet regimens was observed (odds ratio [OR] = 0.65, 95% CI = 0.51–0.82, $p < 0.001$). Conversely, no statistical difference in 1-year survival rates was noted between double and single-agent chemotherapy (OR = 0.78, 95% CI = 0.57–1.06, $p = 0.169$). The incidence of grade 3–4 toxicities did not differ significantly between the arms excluding thrombocytopenia (OR = 1.76, 95% CI = 1.12–2.76, $p = 0.014$).

Hence, monotherapy with third-generation cytotoxic agents including gemcitabine, vinorelbine, docetaxel, and paclitaxel has been recommended as first-line treatment in elderly patients with advanced NSCLC and a PS of 0–2.

Platinum-doublet chemotherapy in non-selected elderly patients with advanced NSCLC

Table 2 shows the results of randomized phase III trials of platinum-doublet chemotherapy as first-line treatments in elderly treatment-naïve patients with advanced NSCLC. Among these phase III trials (Table 2), only one trial demonstrated a statistically significant survival advantage of platinum-doublet chemotherapy compared with single-agent chemotherapy [12]. In this study, patients allocated to the platinum-doublet treatment arm received a combination of carboplatin at an area under the concentration-time curve (AUC) of 6 on day 1 plus paclitaxel 90 mg/m^2 on days 1, 8, and 15 every 28 days, and patients allocated to the single-agent treatment arm received gemcitabine 1150 mg/m^2 or vinorelbine 25 mg/m^2 on days 1 and 8 every 21 days. A survival benefit of 4 months was noted in patients treated with carboplatin-doublet chemotherapy (10.3 months vs. 6.2 months, $p < 0.0001$). By contrast, severe hematologic toxicities (grade 3–4) and treatment-related death occurred more frequently in the combination chemotherapy arm than in the single-agent arm. On the contrary, combination chemotherapy with cisplatin plus docetaxel failed to produce a survival advantage versus single-agent docetaxel in another trial [13]. Patients aged 70 years or older with a PS of 0–1 were randomly assigned to receive cisplatin 25 mg/m^2 on days 1, 8, and 15 every 28 days or docetaxel 60 mg/m^2 on day 1 every 21 days in this study. No significant difference was observed in survival between these groups (13.3 months vs. 14.8 months, HR = 1.18, 95% CI = 0.83–1.69). Severe hematologic toxicities such as neutropenia (grade 3–4) and febrile neutropenia occurred more frequently in the single-agent treatment arm, whereas anorexia and hyponatremia were more common in the doublet treatment arm. Biesma et al. conducted a clinical trial to determine which of two platinum-doublet chemotherapy regimens was associated with the greatest increase in a QOL score [14]. One hundred eighty-one chemotherapy-naïve patients were eligible for this study, and they were randomly assigned to receive carboplatin at an AUC of 5 on day 1 and either gemcitabine 1250 mg/m^2 on days 1 and 8 or paclitaxel 175 mg/m^2 on day 1. There were no significant interactions between QOL scores and the treatment regimen. OS was not significantly different between the treatment arms (8.6 months in the carboplatin plus gemcitabine arm vs. 6.9 months in the carboplatin plus paclitaxel arm, HR = 1.22, 95% CI = 0.89–1.69). Another study reported the efficacy of front-line platinum-doublet chemotherapy in elderly patients with advanced NSCLC [15]. Researchers analyzed three previous clinical trials of platinum-based chemotherapy in elderly chemotherapy-naïve patients with advanced NSCLC. Among 44,985 patients who met the study eligibility criteria, 15,318 received identifiable first-line chemotherapy. The most frequently received chemotherapy regimen was carboplatin plus paclitaxel (6597 cases), followed by carboplatin plus gemcitabine (2190 cases), and carboplatin and docetaxel (1301 cases). The number of patients who received cisplatin-based combination chemotherapy was 690. The

Table 2: Phase III trials of platinum-doublet chemotherapy as a first-line treatment in elderly patients with advanced NSCLC.

Study	PS	Number of patients	Age (years)	Treatment	RR (%)	Median OS	
Quoix et al. [12]	0–2	451	≥70	GEM or VNR	10.2	6.2 mo	HR = 0.64 (95% CI = 0.52–0.78) $p < 0.0001$
				CBDCA+PTX	27.1	10.3 mo	
JCOG0803/WJOG4307L [13]	0–1	221	≥70	DOC	24.6	14.8 mo	HR = 1.18 (95% CI = 0.83–1.69)
				CDDP+DOC	34.4	13.3 mo	
Biesma et al. [14]	0–2	181	≥70	CBDCA+GEM	27	8.6 mo	HR = 1.22 (95% CI = 0.89–1.69)
				CBDCA+PTX	19	6.9 mo	

Abbreviations: NSCLC: Non-small Cell Lung Cancer; RR: Response Rate; OS: Overall Survival; HR: Hazard Ratio; CI: Confidence Interval; GEM: Gemcitabine; VNR: Vinorelbine; CBDCA: Carboplatin; PTX: Paclitaxel; DOC: Docetaxel; CDDP: Cisplatin

10,064 patients who received carboplatin plus paclitaxel, carboplatin plus gemcitabine, or carboplatin plus docetaxel and who had complete data on patient characteristics comprised the study cohort. The median survival times for the three aforementioned treatment arms were 8.0, 7.3, and 7.5 months, respectively. In a multivariable Cox proportional hazard model adjusted for baseline characteristics, both carboplatin plus gemcitabine (HR = 1.10, 95% CI = 1.05–1.16) and carboplatin plus docetaxel (HR = 1.09, 95% CI = 1.03–1.16) were associated with a slightly higher risk of death than carboplatin plus paclitaxel. The researchers concluded that carboplatin-based doublet chemotherapy was useful and tolerable in elderly patients and that the carboplatin plus paclitaxel regimen was associated with slightly better survival than other carboplatin-based combination chemotherapy regimens. Unfortunately, the three trials analyzed in the study were not comparison trials of platinum-doublet chemotherapy versus single-agent chemotherapy, and no assessment of the chemotherapy regimen schedule (e.g., weekly, monthly) was documented in the studies. Previously, two randomized phase III trials comparing platinum-doublet chemotherapy with single-agent chemotherapy as a first-line treatment were performed in patients with a poor PS (=2). The CAPPA-2 study was conducted to examine cisplatin plus gemcitabine versus gemcitabine alone in patients with advanced NSCLC aged 18–70 years [16]. The median OS times were 5.9 months in the platinum-doublet arm and 3.0 months in the single-agent arm (HR = 0.52, 95% CI = 0.28–0.98, $p = 0.039$). Significant longer PFS was noted in the platinum-doublet arm (median PFS, 3.3 months vs. 1.7 months, HR = 0.49, 95% CI = 0.27–0.89, $p = 0.017$). Another trial was conducted to examine carboplatin plus pemetrexed versus single-agent pemetrexed in patients with advanced NSCLC [17]. Platinum-doublet chemotherapy was significantly superior to single-agent chemotherapy in terms of RR, median PFS, and median OS (23.8% vs. 10.3%, $p = 0.032$; 5.8 months vs. 2.8 months, HR = 0.46 [95% CI = 0.35–0.63], $p < 0.001$; and 9.3 months vs. 5.3 months, HR = 0.62 [95% CI = 0.46–0.83], $p = 0.001$, respectively). However, no assessment for elderly patients was documented in these trials. Although several subset analyses of elderly patients in prospective randomized trials of first-line treatments for advanced NSCLC reported a survival benefit of platinum-doublet chemotherapy versus single-agent chemotherapy or comparable survival efficacy to that observed in non-elderly patients, severe adverse events, especially hematological toxicities, were numerically more common in the elderly population [18-20].

Targeted therapy in specific elderly patients with advanced NSCLC

In the last decade, several randomized phase III trials of first-generation EGFR-tyrosine kinase inhibitors (TKIs) including gefitinib and erlotinib in comparison with standard platinum-doublet chemotherapy as first-line treatments demonstrated significant higher RRs and prolonged PFS for advanced NSCLC harboring activating *EGFR* mutations such as exon 19 deletion and L858R mutation [21-24] among patients with a better PS (0–1). However, among these trials, elderly patients 70 years or older were excluded from the WJOG 3405 [21] and NEJ 002 [22] trials. In the OPTIMAL [23] and EUROTAC [24] trials comparing erlotinib with standard platinum-doublet chemotherapy in patients with NSCLC harboring *EGFR* mutations, elderly patients were included, and no negative effects in this population such as lower RR, shorter survival durations, or the development of severe toxicities were documented. To the best of our knowledge, no prospective large-scale trials of those first-generation EGFR-TKIs in elderly patients with *EGFR*-mutated advanced NSCLC have been conducted. However, previous several small prospective phase II trials of these EGFR-TKIs as first-line treatments for elderly patients with *EGFR*-mutated advanced NSCLC reported similar efficacy and tolerability as the results of the aforementioned phase III trials and no negative data have been documented [25-30]. Based on the effectiveness of gefitinib and erlotinib in previous clinical studies, both of these EGFR-TKIs are recommended as first-line treatments in elderly patients with advanced NSCLC harboring activating *EGFR* mutations.

Table 3 presents previous large-scale phase III trials of first-generation EGFR-TKIs combined with platinum-doublet chemotherapy as first-line treatments in non-selected patients with advanced NSCLC compared with chemotherapy. The combination of chemotherapy with EGFR-TKIs did not improve survival, but it resulted in a higher incidence of severe treatment-related toxicities [31-34]. FASTACT-2 was a phase III trial that examined the combination of chemotherapy and erlotinib versus chemotherapy alone for chemotherapy-naïve patients with advanced NSCLC [35]. In this trial, eligible patients received six cycles of chemotherapy (gemcitabine plus carboplatin or cisplatin) with intercalated erlotinib (on days 15–28) or placebo every 4 weeks. All patients assigned to the placebo arm were offered erlotinib as a second-line treatment after confirmed disease progression. Significantly longer PFS and OS were noted in the erlotinib arm compared with the placebo arm (PFS: 7.7 months vs. 6.0 months, HR = 0.57, $p < 0.0001$; OS: 18.3 months vs. 15.2 months, HR = 0.79, $p = 0.042$). A significantly higher RR was observed in the erlotinib arm (43% vs. 18%, $p < 0.0001$). Serious adverse events occurred in 31% of patients in the erlotinib arm and 34% of those in the placebo arm. Treatment-related death occurred in 12 patients in the erlotinib arm, versus seven patients in

Table 3: Phase III trials of EGFR-TKIs combined with platinum-doublet chemotherapy as first-line treatments for unselected patients with advanced NSCLC.

Study	Number of patients	Median Age, years (range)	Treatment	RR (%)	Median PFS or TTP	*p*-value	Median OS	*p*-value
INTACT-1 [31]	365	61 (31–85)	G (500 mg)+CG	50.3	5.5 mo	0.7633	9.9 mo	0.456
	365	59 (34–83)	G (250 mg)+CG	51.2	5.8 mo		9.9 mo	
	363	61 (33–81)	Placebo+CG	47.2	6.0 mo		10.9 mo	
INTACT-2 [32]	347	62 (26–82)	G (500 mg)+CP	30.0	4.6 mo	0.0562	8.7 mo	0.6385
	345	61 (27–86)	G (250 mg)+CP	30.4	5.3 mo		9.8 mo	
	345	63 (31–85)	Placebo+CP	28.7	5.0 mo		9.9 mo	
TRIBUTE [33]	539	63 (24–84)	E+CP	21.5	5.1 mo	0.36	10.6 mo	HR = 0.995 (95% CI = 0.86–1.16) 0.95
	540	63 (26-84)	Placebo+CP	19.3	4.9 mo		10.5 mo	
TALENT [34]	580	61 (26-82)	E+CG	31.5	23.7 wk	HR = 0.98 (95% CI = 0.86–1.11) 0.74	43 wk	HR = 1.06 (95% CI = 0.90–1.23) 0.49
	579	60 (28-84)	Placebo+CG	29.9	24.6 wk		44.1 wk	
FASTACT-2 [35]	226	59 (31-96)	E+CG/CAG	44	7.6 mo	HR = 0.57 (95% CI = 0.47–0.69) <0.0001	18.3 mo	HR = 0.79 (95% CI = 0.64–0.99) 0.042
	225	57 (37-88)	Placebo+CG/CAG	16	6.0 mo		15.2 m	

Abbreviations: EGFR-TKIs: Epidermal Growth Factor Receptor-tyrosine-kinase Inhibitors; NSCLC: Non-small Cell Lung Cancer; RR: Response Rate; PFS: Progression-free Survival; TTP: Time to Progression; OS: Overall Survival; G: Gefitinib; CG: Cisplatin plus Gemcitabine; CP: Carboplatin plus Paclitaxel; E: Erlotinib; CAG: Carboplatin plus Gemcitabine

the placebo arm. In a subgroup analysis based on *EGFR* mutation status, survival and response benefits associated with erlotinib were predominantly observed in the erlotinib arm (PFS: 16.8 months vs. 6.9 months, HR = 0.25, $p < 0.0001$; OS: 31.4 months vs. 20.6 months, HR = 0.48, $p = 0.0092$; RR: 84% vs. 15%, $p < 0.0001$). By contrast, among patients with wild-type *EGFR*, no significant differences in survival and response were recorded between the two groups (PFS: 6.7 months vs. 5.9 months, HR = 0.97, $p = 0.8467$; OS: 14.9 months vs. 12.2 months, HR = 0.77, $p = 0.1612$; RR: 26% vs. 19%, $p = 0.35$). However, no assessment was conducted for elderly patients in these trials of EGFR-TKIs combined with chemotherapy.

Afatinib is a second-generation EGFR-TKI that irreversibly inhibits pan-human epidermal receptor (pan-HER) including EGFR, HER2, and HER4 by covalently binding to the kinase domain of these receptors. The LUX-Lung 3 [36] and 6 [37] studies were randomized phase III trials of front-line afatinib compared with standard platinum-doublet chemotherapy for chemotherapy-naïve patients with advanced NSCLC harboring *EGFR* mutations. Both trials uncovered significant survival and response advantages for afatinib, and the Food and Drug Administration approved the EGFR-TKI as a first-line treatment regimen for patients with advanced NSCLC and activating *EGFR* mutations. Subset analysis in these LUX-Lung trials revealed the similar efficacy of the drug between elderly patients aged 60 years or older and non-elderly patients. Meanwhile, severe treatment-related toxicities (grade 3–5) attributable to afatinib occurred more frequently in the elderly population. To the best of our knowledge, no results of prospective trials of afatinib for elderly patients with advanced *EGFR*-mutated NSCLC have been reported.

Crizotinib is an oral TKI targeting the EML4-ALK fusion gene. Crizotinib has been approved for the optimal treatment for ALK-positive NSCLC based on the results of previous studies [38-39]. A recent phase III trial demonstrated the superiority of front-line crizotinib regarding survival compared with standard platinum-doublet chemotherapy consisting of cisplatin plus pemetrexed in patients with advanced ALK-positive NSCLC [40]. A total of 343 patients were enrolled in this trial, and the median patient age was 52 years (range: 22–76) in the crizotinib arm and 54 years (range: 19–78) in the chemotherapy arm. PFS, which was the primary endpoint, was significantly longer in the crizotinib arm (median, 10.9 months vs. 7.0 months, HR = 0.45, 95% CI = 0.35–0.60, $p < 0.001$). The objective RR was significantly higher in the crizotinib arm than in the chemotherapy arm (74% [95% CI = 67–81%] vs. 45% [95% CI = 37–53%], $p < 0.001$). Based on the results of this trial, crizotinib was approved as a first-line treatment for advanced ALK-positive NSCLC. Among all patients enrolled in this study, 55 were elderly patients aged 65 years or older. The HR favored crizotinib in elderly patients (HR = 0.37, 95% CI = 0.17–0.77). Crizotinib is also recommended as a second-line treatment for ALK-positive NSCLC based on the results of an open-label phase III trial of crizotinib versus standard second-line chemotherapy with pemetrexed or docetaxel in previously treated patients with ALK-positive NSCLC [41]. A total of 347 patients were enrolled in this study, and the median patient age was 51 years (range: 22–81) in the crizotinib arm, 50 years (range: 26–85) in the pemetrexed arm, and 49 years (range: 24–71) in the docetaxel arm. This study met its primary endpoint, with significantly longer PFS recorded in patients treated with crizotinib than in those with chemotherapy (median, 7.7 months vs. 3.0 months, HR = 0.49, 95% CI = 0.37–0.64, $p < 0.001$). The RR was significantly higher in the crizotinib arm than in the chemotherapy arm (65% [95% CI: 58–72%] vs. 20% [95% CI = 14–26%], $p < 0.001$). The most common severe treatment-related toxicities were elevated aminotransferase levels (16%) and neutropenia (13%) in the crizotinib arm. On the contrary, severe neutropenia occurred in 19% of patients treated with chemotherapy. Among all patients included in the safety analysis, the number of elderly patients aged 65 years or older was 50 (27 in the crizotinib arm and 23 in the chemotherapy arm). No significant difference was observed in terms of PFS between the elderly and non-elderly groups (HR = 0.54, 95% CI = 0.27–1.08).

Bevacizumab is an anti-VEGF monoclonal antibody inhibitor that is approved as a first-line treatment in combination with standard chemotherapy in patients with advanced non-squamous cell NSCLC based on the Eastern Cooperative Oncology Group 4599

trial [42]. In this trial, 878 patients were randomized to treatment with chemotherapy plus bevacizumab or chemotherapy alone as a control. The experimental and control arms included 177 and 189 elderly patients aged 65 years or older, respectively. The median PFS was significantly longer in the experimental arm than in the control arm (12.3 months vs. 10.3 months, HR = 0.79 [95% CI = 0.67–0.92], p = 0.003). Additionally, chemotherapy plus bevacizumab significantly improved the RR versus chemotherapy (35% vs. 15%, $p < 0.001$). No significant advantage of chemotherapy plus bevacizumab was observed in terms of OS in elderly patients (HR = 0.89 [95% CI = 0.70–1.14]). Although a subset analysis of elderly patients aged 70 years or older (111 in the experimental arm and 113 in the control arm) uncovered a trend toward a higher RR and longer PFS in favor of chemotherapy plus bevacizumab (29% vs. 17%, p = 0.067; median PFS: 5.9 months vs. 4.9 months, p = 0.063), OS was similar (11.3 months vs. 12.1 months, p = 0.4). Meanwhile, severe toxicities including treatment-related death were more common in the experimental arm than in the control arm (87% vs. 61%, $p < 0.001$) [43]. The AVAiL study was a randomized phase III trial that evaluated the efficacy and safety of two different doses of bevacizumab (7.5 and 15 mg/kg) combined with platinum-doublet chemotherapy as a first-line treatment compared with placebo for patients with advanced non-squamous cell NSCLC [44]. Significant longer PFS was noted in the low- and high-dose groups (median, 6.7 and 6.5 months, respectively) than in the placebo group (6.1 months, p = 0.003 and 0.03, respectively). The objective RRs of the placebo, low-dose, and high-dose groups were 20.1, 34.1, and 30.4%, respectively. The incidence of severe treatment-related toxicities was similar across the arms. A retrospective subgroup analysis of the AVAiL trial was performed to assess the efficacy and safety of bevacizumab combined with chemotherapy in elderly patients aged 65 years or older [45]. Among 1043 patients enrolled in AVAiL, the outcomes of 304 elderly patients were reviewed. Significant longer PFS was noted among patients treated with bevacizumab plus chemotherapy than among those treated with chemotherapy (low-dose group vs. placebo group: HR = 0.71, p= 0.023; high-dose group vs. placebo group: HR = 0.84, p = 0.25). The objective RRs were 40, 29, and 30% in the low-dose, high-dose, and placebo groups, respectively. OS was similar between the experimental and control arms. No particular safety signals were noted in the elderly population. The MO19390 trial was an international open-label, single-arm study that assessed the safety and efficacy of bevacizumab combined with standard chemotherapy as a first-line treatment in patients with advanced or recurrent non-squamous cell NSCLC [46]. In this study, a preplanned subgroup analysis was conducted to evaluate the outcomes of elderly patients aged 65 years or older. Among 2212 patients in the MO19390 study population, 623 elderly patients were evaluated. The median OS, time to progression (TTP), and RR were 14.6 months, 8.2 months, and 49.3%, respectively, in elderly patients and 14.6 months, 7.6 months, and 52.4%, respectively, in non-elderly patients. These results were similar for both groups. Severe treatment-related adverse events occurred in 45.3% of elderly patients and 34.7% of non-elderly patients. Similar results were noted in a post hoc comparison of elderly patients aged 70 years or older and non-elderly patients. TTP, OS, and RR were 8.6 months, 14.6 months, and 49%, respectively, in elderly patients and 7.7 months, 14.6 months, and 52%, respectively, in non-elderly patients. These results were similar for elderly patients aged 70 years or older and younger patients. The incidence of adverse events of special interest was comparable. The PointBreak study was a randomized phase III trial of different standard platinum-doublet chemotherapy regimens (carboplatin plus pemetrexed and carboplatin plus paclitaxel) plus bevacizumab followed by maintenance bevacizumab with or without chemotherapy [47]. Although significantly prolonged PFS was noted in patients treated with carboplatin plus pemetrexed combined with bevacizumab, no significant difference was observed in terms of OS between the groups. Among 939 patients enrolled in this study, 247 patients were elderly patients aged 70 or older. No significant differences in PFS and OS were noted (PFS: HR = 0.98; OS: HR= 0.90).

Although several retrospective and subgroup analyses of elderly patients were performed in previous phase III trials of targeted agents, to the best of our knowledge, no prospective randomized phase III trials comparing targeted agents alone with targeted agents combined with chemotherapy as first-line treatments for elderly patients with advanced NSCLC have been conducted.

Discussion

Previous clinical data indicated that although severe adverse events would be more frequently observed in patients treated with combination chemotherapy consisting of two different types of third-generation cytotoxic agents, combination regimens did not confer significant survival advantages compared with single-agent chemotherapy in elderly patients with NSCLC. Thus, single third-generation cytotoxic agents including gemcitabine, docetaxel, vinorelbine, and paclitaxel should be considered appropriate first-line treatments in non-selected elderly patients with a PS of 0–2. Previous phase III studies of pemetrexed as a first- or second-line treatment demonstrated the non-inferiority efficacy of pemetrexed as well as its statistically better tolerability versus standard chemotherapy for advanced NSCLC [48,49]. Two retrospective studies on these trials of pemetrexed were conducted. One study revealed the favorable efficacy of pemetrexed for NSCLC in patients with non-squamous cell histology [50]. Another study uncovered a longer TTP, longer survival, and a more favorable toxicity profile of pemetrexed for elderly patients compared with docetaxel [51]. Thus, pemetrexed may be a reasonable first-line treatment option in elderly patients with non-squamous NSCLC. However, no prospective randomized studies have examined whether pemetrexed would be more useful than third-generation cytotoxic agents for elderly chemotherapy-naïve patients with advanced non-squamous NSCLC.

Platinum-doublet chemotherapy combined with third-generation cytotoxic agents may be more promising as first-line treatments in elderly patients, especially in those with a better PS (0–1). However, considering the frequency of severe hematological adverse events and treatment-related death, first-line treatment regimens using standard platinum-doublet chemotherapy with the same schedule and dose as those used in non-elderly patients would not be warranted for elderly patients. Based on the two aforementioned clinical trials for advanced NSCLC in patients with a PS of 2, although platinum-doublet chemotherapy regimens significantly improved survival versus single-agent chemotherapy, higher rates of toxicities and treatment-related death were observed in the platinum-doublet chemotherapy arm. Whereas both trials confirmed the positive effect of platinum-

doublet chemotherapy for patients with a PS of 2, few patients have been treated with this regimen in practice. Indeed, chemotherapy tends to be avoided in patients with a poor PS and elderly patients because of apprehension regarding the higher incidence of severe treatment-related toxicities. However, elderly patients comprise a heterogeneous population with significant differences in the level of organ function, number of complications, and other variables. Thus, it is difficult to state that the results of the two aforementioned trials of patients with a PS of 2 are applicable to elderly patient populations.

Generally, physicians have concerns about treatment strategies using cytotoxic agents for older patients because of decreasing tolerability to treatment with age. Indeed, only a small percentage of elderly patients were eligible for inclusion in clinical trials of new agents and regimens [52-54]. Thus, elderly patients treated with protocol chemotherapy may not be representative of the entire elderly patient population. Indeed, inevitably decreases in organ function, especially bone marrow reserves, with age and increases in the number of complications such as cardiovascular disease and pulmonary disease are obstacles to treatment with cytotoxic chemotherapy. The definition of elderly patients was different in each of the aforementioned phase III trials and retrospective studies. An age of 70 years may be considered the threshold age of cell senescence after which the rate of age-related changes increases [55]. Although platinum-doublet chemotherapy regimen may be an optimal first-line treatment regimen in elderly patients with advanced NSCLC, further studies are needed to define the most appropriate regimen and confirm its tolerability. The JCOG1210/WJOG7813L study (UMIN000011460) of docetaxel versus carboplatin plus pemetrexed followed by pemetrexed as a first-line treatment in patients aged 75 years or older with advanced non-squamous NSCLC is ongoing. Physicians make treatment decisions for elderly patients with NSCLC in consideration of PS, physical and organ function, level of complication, activity, and mental state. Elderly patients comprise a heterogeneous population, and thus, some patients have a similar tolerability for standard first-line chemotherapy as non-elderly patients. Thus, a viable tool to assist physicians in assessing the tolerability of elderly patients for chemotherapy is needed. Some investigators developed valid and reliable geriatric assessment tools [56,57]. However, these tools are complicated and difficult to use in practically situations.

First-generation EGFR-TKIs including gefitinib and erlotinib have similar efficacy and tolerability in elderly patients with advanced NSCLC and activating *EGFR* mutations. These agents have been proven to palliate clinical symptoms immediately in elderly patients regardless of their PS. Afatinib may have similar activity as first-generation EGFR-TKIs, and it may be an optimal first-line regimen similarly as other first-generation EGFR-TKIs with careful management for skin toxicities and diarrhea in elderly patients with *EGFR*-mutated NSCLC. Although the LUX-Lung 7 study (NCT01466660), which is a phase IIb head-to-head trial comparing afatinib with gefitinib in chemotherapy-naïve patients harboring *EGFR*-mutated NSCLC, is ongoing, no prospective trials comparing these three EGFR-TKIs have been conducted for elderly patients with *EGFR*-mutated NSCLC.

Trials of EGFR-TKIs plus chemotherapy have rarely uncovered improvements in survival excluding the FASTACT-2 trial. Preclinical studies demonstrated that EGFR-TKIs cause G1 cycle arrest in wild-type *EGFR* cancer cell lines, inhibiting the cell cycle-dependent cytotoxic effects of chemotherapy and induction of apoptosis in cell lines with *EGFR* mutations [58,59]. Based on these preclinical data, researchers examined new treatment regimens consisting of intercalated erlotinib combined with chemotherapy in the FASTACT-2 study. However, intercalated erlotinib plus chemotherapy did not improve survival in patients with wild-type *EGFR*. Although significantly longer survival was noted in the experimental arm with this new treatment regimen, its positive result should be largely attributed to the longer survival time of erlotinib responders. Further investigations will be needed to assess whether intercalated combinations of EGFR-TKI and chemotherapy are superior to EGFR-TKI monotherapy and whether these new regimens would be suitable first-line treatments for elderly patients with *EGFR*-mutated NSCLC.

Whereas crizotinib is a promising first-line therapy for ALK-positive NSCLC, only a few patients experienced a benefit of the targeted agent. The ALK fusion gene appears to be present in approximately 3–6% of non-selected patients with NSCLC, and it is significantly more common in never-smokers than in smokers and in non-elderly patients than in elderly patients [60-66]. Although it is difficult to perform large-scale clinical trials of crizotinib as first-line treatment for elderly patients with ALK-positive NSCLC, further assessments are needed to evaluate the efficacy and tolerability of crizotinib as a first-line treatment in elderly patients with the ALK fusion gene.

Bevacizumab combined with platinum-doublet chemotherapy is approved as a first-line treatment in patients with advanced non-squamous NSCLC. However, no subset analysis of elderly patients in previous phase III trials demonstrated an OS benefit despite a higher RR and longer PFS because of significantly higher incidences of severe treatment-related toxicity. Combination treatment with platinum-doublet chemotherapy plus bevacizumab may potentially confer a survival benefit according as a proper chemotherapy regimen for elderly patients with non-squamous NSCLC. Even if this devised combination regimen does not meaningfully prolong overall survival, improvements in PFS and response conferred by the therapy may improve QOL in elderly patients if the incidence of treatment-related adverse events is acceptable. In the future, prospective clinical trials should be conducted to assess the efficacy and tolerability of bevacizumab combined with platinum-doublet chemotherapy, single third-generation cytotoxic agent monotherapy, or pemetrexed.

Conclusion

Third-generation cytotoxic agents are recommended as first-line treatments for elderly patients with advanced NSCLC, and clinical data support the potentially equivalent efficacy and better tolerability of pemetrexed compared to those agents. Whereas first-generation EGFR-TKIs, especially gefitinib, are commonly administered as first-line therapies in elderly patients harboring activating *EGFR* mutations irrespective of their clinical condition, further assessment of the efficacy and tolerability of afatinib and crizotinib in select elderly patients with NSCLC is needed. Although platinum-doublet chemotherapy and combined treatment with targeted agents plus chemotherapy may be promising treatment regimens, further

investigations are needed to define the treatment schedule and dose for elderly patients who are suitable for chemotherapy and validate its superiority to standard single-agent chemotherapy or monotherapy with targeted agents. To that end, the establishment of a suitable geriatric assessment tool for practical use is urgently needed because of the heterogeneity of elderly patient populations.

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