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Do Older Patients with Metastatic Non-Small Cell Lung Cancer Also Benefit from First-Line Platinum-Based Doublet Chemotherapy?:

Observations from a Pooled Analysis of 730 Prospectively-Treated Patients (Alliance Study A151622)

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Abstract

Objective: This study sought to define the role of first-line platinum-based doublet chemotherapy in older non-small cell lung cancer (NSCLC) patients.

Methods: We analyzed three first-line NSCLC trials: CALGB 9730, CALGB 30203, and CALGB 30801, which tested carboplatin and paclitaxel; carboplatin and gemcitabine; and carboplatin with either pemetrexed or gemcitabine, respectively. Overall survival was the primary endpoint. Age-based comparisons with a cutpoint of 65 years were performed with Cox proportional hazards models with adjustments for sex, tumor histology, cancer stage, chemotherapy, and smoking history and after stratifying by performance score. Secondary endpoints were grade 3–5 adverse events, chemotherapy cycles completed, and whether toxicity prompted chemotherapy discontinuation.

Results: 730 patients were included; 337 (46%) were 65+ years of age. No statistically significant difference in survival was observed for older (≥65) versus younger patients (HR = 1.096; 95% CI = (0.94, 1.28); p=0.25). A trend emerged with increased odds of a grade 3–5 adverse event for patients ≥65 years versus <65 years (OR =1.52; 95% CI = (0.99, 2.31); p = 0.05). The proportion of completed chemotherapy cycles was marginally lower in older patients (difference = –5%; 95% CI = (–9, 0.2); p=0.06) for those ≥65 years versus <65 years, but no statistically significant difference occurred in the rate of chemotherapy discontinuation for toxicity (OR = 1.4; 95% CI = (0.85, 2.19); p=0.21) for patients ≥65 years versus <65 years. A cutpoint of 70 years yielded similar results.

Conclusion: These findings support carboplatin doublet-based chemotherapy in select older patients with advanced NSCLC.

Keywords

lung cancer; older patients; geriatric oncology; carboplatin; chemotherapy

INTRODUCTION

Guidelines endorse first-line, platinum-based doublet chemotherapy in select, older non-small cell lung cancer patients.[1] However, in older patients, the role of first-line platinum-based doublet chemotherapy has not been fully defined. Although a 451-patient randomized phase III trial in older non-small cell lung cancer patients from 70 to 89 years of age demonstrated a survival advantage (hazard ratio (HR): 0.60; p=0.0001) with weekly carboplatin and paclitaxel versus single agent gemcitabine or vinorelbine, this platinum doublet yielded greater toxicity, including neutropenia and asthenia. Similarly, Wang and others conducted a meta-analysis of 11 randomized controlled trials in older patients and reported that platinum-based doublet chemotherapy yields superior survival compared to single agent chemotherapy (HR: 0.89; 95% confidence interval (CI) = (0.83, 0.95); p =0.001) but higher rates of severe anemia, thrombocytopenia, and fatigue. Interestingly, in this same meta-analysis, these investigators reported that non-platinum-based doublet therapy offered no survival advantage over single agent therapy (HR = 0.93; 95% CI = (0.86, 1.01); p =0.078), thus further showing the importance of platinum-based chemotherapy in older non-small cell lung cancer patients.[2] This trade-off of modest survival in exchange

for increased toxicity suggests a need to further study platinum-based doublet chemotherapy in the first-line setting in older non-small cell lung cancer patients.

The imperative to further study this fundamental therapeutic question in older patients is underscored by shifting age demographics and the reality that recent targeted or immunotherapy-based cancer treatment pertain only to a subgroup of non-small cell lung cancer patients. The median age of patients diagnosed with non-small cell lung cancer has increased over time to 70 years of age. Thus, this malignancy is a disease of older patients and underscores the practical relevance of learning how best to treat these patients. Furthermore, although therapeutic interventions that target driver mutations and that use immunotherapy interventions have markedly improved clinical outcomes, such approaches provide therapeutic benefit to only one third of patients, leaving conventional therapy the first-choice option for a sizable majority of lung cancer patients. This last point is only further emphasized by results from the KEYNOTE 21 trial that showed higher tumor response rates and longer progression-free survival with the addition of pembrolizumab to carboplatin-based chemotherapy, once again confirming conventional chemotherapy as a viable first-line option for a sizable majority of lung cancer patients.[3]

In this context, the role of platinum-based doublet therapy remains relevant and merits further study in older cancer patients. Here we rely on three multi-institutional, prospectively-conducted trials to generate an individual patient pooled data set, which enabled us to evaluate survival and adverse events from platinum-based doublet chemotherapy in older lung cancer patients and their younger counterparts.

METHODS

Overview.

This pooled analysis focused on three prospective, first-line clinical trials for patients with advanced non-small cell lung cancer: 1) CALGB 9730 randomly assigned 561 patients to carboplatin plus paclitaxel (carboplatin area under the curve (AUC) 6 mg/ml/min on day 1 and paclitaxel 225 mg/m²) versus paclitaxel alone and showed that combination therapy improved outcomes in age-unspecified patients; a preplanned subset analysis by age showed a 1-year survival for combination chemotherapy of 35% versus 31% for single-agent therapy; HR = 0.84, P = .29 in patients >70 of age; for patients ≤70 of age, the 1-year survival was 38% for combination chemotherapy and 33% for single-agent chemotherapy, respectively (HR=0.98, P=.50.); 2) CALGB 30203 randomly assigned 134 patients to carboplatin and gemcitabine (carboplatin AUC 5.5 mg/ml/min on day 1 and gemcitabine 1000 mg/m² on day 1 and 8) with or without zileuton (a 5-lipoxygenase inhibitor) or celecoxib (a cyclooxygenase inhibitor) or zileuton plus celecoxib; this study showed no benefit with the addition of eicosanoid inhibition; and 3) CALGB 30801 randomly assigned 312 patients to carboplatin plus pemetrexed (carboplatin AUC 6 on day 1 and pemetrexed 500 mg/m² on day 1) for non-squamous histology or carboplatin plus gemcitabine (carboplatin AUC 5.5 on day 1 with gemcitabine 1000 mg/m² on day 1 and 8) for squamous cell histology with or without celecoxib, which showed no improved outcomes with celecoxib. [4–6] Because each individual trial above had received institutional review board (IRB) approval, no IRB approval was needed for the current analyses. Importantly, the current

analysis included both older and younger patients but focused exclusively on those who had received platinum-based doublet therapy.

Definition of Endpoints.

The primary endpoint of the current study was overall survival, and the analysis plan entailed an age-based comparison with adjustments for sex, tumor histology, cancer stage (IIIB and IV), administered chemotherapy regimen, and smoking history with stratification by performance score. These variables were selected based on their impact on prognosis.[7] Secondary endpoints were also evaluated by means of age-based group comparisons and consisted of the incidence of grade 3–5 adverse events and the proportion of chemotherapy cycles completed (no more than 6 cycles had been planned in all three studies) as well as whether chemotherapy toxicity had prompted discontinuation.

Statistical Analyses:

Two sets of analyses were undertaken. The primary analyses compared outcomes of patients age 65 years or greater to those younger than 65. The secondary analyses compared outcomes between patients with age 70 years or greater to those younger than 70. For the primary endpoint, the event is death from any cause, and survival is the time from trial enrollment to death or last follow up. The survival probabilities were estimated separately by age group using the Kaplan-Meier estimator. Cox proportional hazards models were used to compare survival, with age group as the main effect and with sex, tumor histology (adenocarcinoma versus squamous cell carcinoma versus other), performance score, cancer stage (IIIB versus IV versus other), administered chemotherapy regimen, and smoking history. The proportional hazards assumption was tested for all variables. Performance score did not meet the proportional hazards assumption and was included as a stratification factor in the final models. For Grade 3–5 adverse events, the probability of experiencing at least one grade 3–5 adverse event was estimated by age group and was compared between groups with logistic regression with adjustment for potential confounding factors. Adjustment factors were selected using a stepwise selection procedure from the list of covariates included in the Cox model. The decision was made to focus only on grade 3 or worse adverse events, as the uniformly high incidence of low grade adverse events detracted from the clinical relevance of group comparisons. The proportion of chemotherapy cycles completed was summarized by mean (standard deviation) and median (range) by age group and was compared between the age groups using linear regression with age group as the main effect and adjusting for potential confounding factors, which were chosen with a stepwise selection procedure. The probability of treatment discontinuation due to toxicity was compared using the same method described for grade 3 or worse adverse events. Two-way interaction between the main effect and all other covariates were examined in all models, and none was found statistically significant.

RESULTS

Patient Demographics.

A total of 730 patients, who received carboplatin and paclitaxel (n=284), carboplatin and gemcitabine (n=290), or carboplatin and pemetrexed (n=156), are included in this report.

Three hundred thirty-seven (47%) were 65 years of age or older at the time of original trial enrollment, and 192 (26%) were 70 years of age or older (Table 1). All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 as well as normal organ and marrow function at the time of trial enrollment.

Overall Survival.

In a univariate analysis, no difference in overall survival was observed between older and younger patients (Figure 1). The one-year overall survival rate was 38.9% (95% confidence interval (CI): 33.9%, 44.6%) in the patients 65 years of age or older and 47.7% (95% CI: 43.0%, 53.0%) in younger patients. The two-year overall survival rate was 16.5% (95% CI 12.9–21.1) in patients 65 years of age or older and 15.7% (95% CI 12.4–19.9%) in younger patients. The three-year overall survival rate was 7.1% (95% CI: 4.8%, 10.7%) in patients 65 years of age or older and 8.1% (CI: 5.7%, 11.4%) in younger patients.

In a multivariate analysis, no difference in overall survival was observed between older and younger patients after adjusting for sex, histology, disease stage, chemotherapy, and smoking status and after stratifying by performance score. In patients who were 65 years of age or older versus younger, the hazard ratio (HR) was 1.10 (95% CI = (0.94, 1.28); $p=0.25$). There was no statistically significant interaction between age group and other variables in the model. The comparison of age-based groups based on the cut point of 70 years of age yielded similar survival results with a HR of 1.16 (95% CI: 0.97, 1.38; $p=0.10$), again with no statistically significant interactions between age groups and other variables. Within the multivariate models, male gender, squamous cell histology, and previous or current smoking status were associated with inferior survival. Confirmatory analyses that included age as four equally-divided age categories by years did not demonstrate differences in overall survival (Figure 2).

Adverse Events.

There were no differences in rates of grade 3–5 adverse events between age groups. The rates of grade 3–5 adverse events were 84.9% and 79.6% in patients 65 years of age or older and in younger patients, respectively ($p=.07$). The rates of grade 3–5 adverse events were 85.4% and 80.9% in patients 70 years of age or older and in younger patients, respectively ($p=0.16$). On multivariable logistic regression, after adjusting for chemotherapy, smoking status, histology, and performance score, the odds ratio of grade 3–5 adverse events in patients 65 years of age or older versus younger was 1.518 and trended towards significance (95% CI = (0.998, 2.310); $p = 0.0511$). However, there was no difference in the odds of grade 3–5 adverse events in the 70 years vs. <70 year group (OR = 1.36; 95% CI = (0.83, 2.21); $p=0.22$).

Rates of Completion of 6 Cycles Chemotherapy.

All groups completed close to 70% of the intended 6 cycles of chemotherapy. The most common reasons for discontinuation included disease progression (50%), death (10%), and toxicity (10%). On average, patients 65 years of age or older completed 65% of chemotherapy cycles compared to 69% in younger patients (Table 2). In multivariate linear regression modeling adjusted for baseline performance score (worse performance score was

associated with less chemotherapy administration), the proportion of chemotherapy cycles completed appeared marginally lower in older patients (difference = -0.05 ; 95% CI = $(-0.09, 0.002)$; $p = 0.06$ for the 65 years of age or older group versus younger patient comparison; difference = -0.06 ; 95% CI = $(-0.11, 0.008)$; $p = 0.02$ for the 70 years of age or older group versus younger patient comparison).

Based on age, there was no difference in the rate of chemotherapy discontinuation due to toxicity. The rate of discontinuation of chemotherapy due to toxicity was 12.2% and 9.2% in patients who were 65 years of age or older versus younger. Similarly, the rate of discontinuation of chemotherapy due to toxicity was 13.5% and 9.5% in patients who were 70 years of age or older versus younger. In multivariable logistic regression adjusted for sex, no significant difference in discontinuation of chemotherapy due to toxicity was observed based on age. The odds ratio for discontinuation of chemotherapy due to toxicity for patients 65 years of age or older versus younger was 1.36 (95% CI = $(0.85, 2.19)$; $p=0.21$) with similar findings observed with the age cut point of 70 years.

DISCUSSION

Chemotherapy remains an important therapeutic option for most patients with advanced non-small cell lung cancer – even in the age of targeted therapy and immunotherapy. The current study provides further clarity to the fundamental question of the role of first-line platinum-based doublet therapy in older patients. Previous large studies have yielded conflicting conclusions.[8–13] For example, the Eastern Cancer Oncology Group (ECOG) undertook a secondary analysis of a randomized controlled trial of 4 platinum-based doublet (carboplatin- and cisplatin-based) chemotherapy regimens for advanced non-small cell lung cancer and showed comparable survival and toxicity between patients 70 years of age or older ($n=227$) and those younger ($n=912$).[10] In contrast, a pooled analysis from the Southwest Oncology Group (SWOG) included 616 patients, 122 (20%) of whom were 70 years of age or older and reported that overall survival was inferior in older patients compared to younger patients (7 months versus 9 months; $p=0.04$, respectively).[8] Moreover, there was no statistical difference in the number of chemotherapy cycles completed ($p=0.06$), but maximum grade 3–5 toxicities were more common among older patients (94% versus 87%; $p=0.04$). Within the context of these two, contradictory multi-institutional studies, the current study tips the balance in favor of prescribing first-line platinum-based doublet therapy to fit older non-small cell lung cancer patients with no driver mutations and with no first-line, single agent immunotherapy option.

Of note, this pooled analysis has limitations. First, we focused on older studies, two of which -- CALGB 9730 and CALGB 30203 -- did not distinguish tumor histology. By today's standards, tumor histology influences choice of chemotherapy and hence clinical outcome. Moreover, molecular analyses of EGFR, ALK, or ROS-1 were not common practice when each of these studies was actively enrolling patients. As a result, a subgroup of patients treated on these studies might not have been candidates for first-line chemotherapy with the chosen platinum-based doublet, a situation that may lessen the relevance of our data to current day management of non-small cell lung cancer. Second, older patients who enroll on clinical trials in general appear to be more fit than other

patients. This factor might influence how the conclusions of the current study are borne out in clinical practice. Furthermore, these studies did not include geriatric assessments which could allow us to better understand the level of “fitness” and the predictors of toxicity. Older patients who are less physically fit remain suboptimal candidates for platinum-based doublet chemotherapy.

The current study also has several advantages. It evaluated older patients who received therapies with a carboplatin backbone as opposed to pooling patients who received either carboplatin or cisplatin in the same analyses. In effect, the therapeutic approach in the current study was uniform and thereby helped contribute clear direction on the clinical management of older lung cancer patients. Finally, the definition of “older” continues to be debated. Importantly, our analysis used two commonly employed definitions and further pursued confirmatory analyses with four finer categories of age, and still did not observe major comparative survival differences based on age.

In summary, the current study suggests that first-line, platinum-based double chemotherapy can be considered in fit older patients who are candidates for chemotherapy for non-small cell lung cancer. These findings further emphasize the point that age alone should not be a barrier to cancer treatment. In future studies and in clinical practice, it will be important to also incorporate geriatric assessments in addition to other prognostic and predictive factors when administering chemotherapy older patients to understand how to best identify those who can benefit from chemotherapy and who may be at greater risk for notable toxicity.

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Figure 1: Overall Survival

No statistically significant differences in overall survival were observed based on comparisons between age groups.

Figure 2: Confirmatory Overall Survival Data Based on Subgroup Analyses
In confirmatory analyses that included 4 different age groups, no statistically significant differences in survival were observed.

Table 1:

Patient Demographics

	< 65 years (N=393)	>= 65 years (N=337)	p value	< 70 years (N=538)	>= 70 years (N=192)	p value
Sex			0.77 ^I			0.13 ^I
Male	242 (61.6%)	204 (60.5%)		320 (59.5%)	126 (65.6%)	
Female	151 (38.4%)	133 (39.5%)		218 (40.5%)	66 (34.4%)	
Race			0.21 ^I			0.05 ^I
White	313 (79.6%)	284 (84.3%)		429 (79.7%)	168 (87.5%)	
Black or African American	56 (14.2%)	34 (10.1%)		75 (13.9%)	15 (7.8%)	
Other	24 (6.1%)	19 (5.6%)		34 (6.3%)	9 (4.7%)	
Performance Score			0.36 ^I			0.54 ^I
0	129 (32.8%)	115 (34.1%)		181 (33.6%)	63 (32.8%)	
1	221 (56.2%)	175 (51.9%)		295 (54.8%)	101 (52.6%)	
2	43 (10.9%)	47 (13.9%)		62 (11.5%)	28 (14.6%)	
Histology			0.18 ^I			0.11 ^I
Adenocarcinoma	243 (61.8%)	186 (55.2%)		327 (60.8%)	102 (53.1%)	
Squamous Cell Carcinoma	81 (20.6%)	84 (24.9%)		112 (20.8%)	53 (27.6%)	
Other	69 (17.6%)	67 (19.9%)		99 (18.4%)	37 (19.3%)	
Cancer Stage			0.50 ^I			0.72 ^I
IIIB	55 (14.0%)	43 (12.8%)		73 (13.6%)	25 (13.0%)	
IV	298 (75.8%)	267 (79.2%)		413 (76.8%)	152 (79.2%)	
Other	40 (10.2%)	27 (8.0%)		52 (9.7%)	15 (7.8%)	
Smoking Status			0.0055 ^I			0.03 ^I
Missing	85	52		105	32	
Never Smoked	14 (4.5%)	30 (10.5%)		26 (6.0%)	18 (11.3%)	
Smoked (Current or Past)	294 (95.5%)	255 (89.5%)		407 (94.0%)	142 (88.8%)	
Chemotherapy			0.27 ^I			0.40 ^I
Carboplatin + Gemcitabine	167 (42.5%)	123 (36.5%)		221 (41.1%)	69 (35.9%)	
Carboplatin + Pemetrexed	80 (20.4%)	76 (22.6%)		110 (20.4%)	46 (24.0%)	
Carboplatin + Paclitaxel	146 (37.2%)	138 (40.9%)		207 (38.5%)	77 (40.1%)	

^I Chi-Square

Table 2:

Proportion of Chemotherapy Cycles Completed By Age Groups

	< 65 years	>= 65 years	p-value	< 70 years	>= 70 years	p-value
n	380	329		520	189	
Mean Proportion of completed chemo	0.69	0.65		0.69	0.63	
Median (Min - Max) Proportion of completed chemo	0.83 (0.00–1.00)	0.67 (0.17–1.00)	0.08	0.75 (0.00–1.00)	0.67 (0.17–1.00)	0.02

Table 3:

Grade 3–5 Adverse Event Rates

	< 65 years	>= 65 years	p-value	< 70 years	>= 70 years	p-value
n	393	337	0.07	538	192	0.16
Frequency of adverse events (%)	313 (79.6%)	286 (84.9%)		435 (80.9%)	164 (85.4%)	