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ORIGINAL REPORT

Age and Comorbidity As Independent Prognostic Factors in the Treatment of Non–Small-Cell Lung Cancer: A Review of National Cancer Institute of Canada Clinical Trials Group Trials

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ABSTRACT

Purpose
This study analyzed patients enrolled in two large, prospectively randomized trials of systemic chemotherapy (adjuvant/palliative setting) for non–small-cell lung Cancer (NSCLC). The main objective was to determine if age and/or the burden of chronic medical conditions (comorbidity) are independent predictors of survival, treatment delivery, and toxicity.

Patients and Methods
Baseline comorbid conditions were scored using the Charlson comorbidity index (CCI), a validated measure of patient comorbidity that is weighted according to the influence of comorbidity on overall mortality. The CCI score (CCIS) was correlated with demographic data,(ie, age, sex, race), performance status (PS), histology, cancer stage, patient weight, hemoglobin, alkaline phosphatase, lactate dehydrogenase, outcomes of chemotherapy delivery (ie, type, total dose, and dose intensity), survival, and response.

Results
A total of 1,255 patients were included in this analysis. The median age was 61 years (range, 34 to 89 years); 34% of patients were elderly (at least 65 years of age); and 31% had comorbid conditions at randomization. Twenty-five percent of patients had a CCIS of 1, whereas 6% had a CCIS of 2 or greater. Elderly patients were more likely to have a CCIS equal to or greater than 1 compared with younger patients (42% *v* 26%; $P < .0001$), as were male patients (35% *v* 21%; $P < .0001$) and patients with squamous histology (36% *v* 29%; $P = .001$). Although age did not influence overall survival, the CCIS appeared prognostic (CCIS 1 *v* 0; hazard ratio 1.28; 95% CI, 1.09 to 1.5; $P = .003$).

Conclusion
In these large, randomized trials, the presence of comorbid conditions (CCIS ≥ 1), rather than age more than 65 years, was associated with poorer survival.

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INTRODUCTION

The incidence of non–small-cell lung cancer (NSCLC) increases with age; 60% occur in patients aged 60 years and older, and 30% to 40% occur in patients aged 70 years and older.[1,2] The median age of individuals diagnosed with NSCLC in developed countries is 68 years.[3] Eighty-five percent of patients either present with or eventually will develop advanced or recurrent NSCLC. In large meta-analyses, the use of chemotherapy in addition to best supportive care (BSC) has been shown to improve overall survival (OS) compared with BSC alone.[4,5] Survival benefits from chemotherapy have also been demonstrated in trials designed specifically for elderly patients[6,7]. Despite this, elderly patients are often denied therapy, prematurely discontinued from therapy, and excluded from clinical trials because of perceptions that elderly patients are unable to tolerate aggressive chemotherapy and are more likely to suffer increased toxicity with a resultant poor quality of life.[8] However, many studies demonstrate that the elderly patient with a good performance status (PS) can tolerate chemotherapy that has similar toxicity and benefits as nonelderly patients.[9-12]

Although the definition of elderly is the subject of some debate, two benchmarks are often used—peopled either 65 years and older[13] or 70 years and

older.[9,14] The age of 70 years has been described as the lower boundary of senescence, because the incidence of age-related organ dysfunction and the development of comorbid conditions increase sharply between ages 70 and 75 years.[15] The clinical significance of the relationship between age and comorbid conditions is complex in patients with cancer.[16] Although chronologic age is associated with certain age-related conditions,[17] chronologic age may not be as clinically relevant as physiologic age, which also takes into account the burden of chronic disease (comorbidity).[18]

The measurement of comorbidity is challenging. Several scales for determining the burden of illness in a particular patient have been explored for use in an oncology setting.[19] The Charlson comorbidity index (CCI) was developed based on a longitudinal study of 559 patients who were admitted to a medical service during a 1-month period, and it has been validated for predicting major complications of surgery in patients with resectable, stages IA to IIIB NSCLC.[20] The sum of the weighted scores of all the comorbid conditions is used to develop a CCI score (CCIS).[21]

We report here the results of a pooled analysis of two large, prospectively randomized trials of systemic chemotherapy conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) that examined the relationship between age and comorbidity—specifically, whether age and/or comorbidity are predictive of chemotherapy-related toxicity and whether age and/or comorbidity are independent predictors of outcome.

PATIENTS AND METHODS

Patients

BR 18 was a randomized, phase II/III study of 774 patients with advanced NSCLC[22] that compared paclitaxel and carboplatin plus placebo (n = 386) with the same regimen plus BMS-275291 (n = 388), an oral matrix metalloproteinase inhibitor (MMPI). Patients were to receive a maximum of eight cycles of chemotherapy but could continue oral MMPI or placebo thereafter until progression or unacceptable toxicity. JBR 10 was a study in which 482 patients with completely resected, stage IB or II NSCLC were randomly assigned to adjuvant vinorelbine and cisplatin chemotherapy (n = 242) or to observation alone (n = 240).[23] Four cycles of vinorelbine/cisplatin were planned.

CCIS, Toxicity, and Objective Response

Baseline medical conditions and medications were scored using the CCI[21] (Table A1). Laboratory parameters and adverse events were graded using the National Cancer Institute Common Toxicity Criteria Expanded Common Toxicity Criteria (in JBR 10) and version 2.0 of the National Cancer Institute Common Toxicity Criteria toxicity scale (in BR 18). All adverse events, irrespective of causality, were included in the analyses. Objective response (in BR 18 only) was evaluated using the Response Evaluation Criteria In Solid Tumors guidelines.

Chemotherapy and Dose Intensity

For each drug, the total dose administered was calculated and was summarized by median, minimum, and maximum for each group.

Statistical Considerations

OS was defined as the time from randomization to death or was censored at the last known alive date. Progression-free survival (PFS) was defined as the time from randomization to the time of documented disease progression or death, whichever came first. Disease-specific survival (DSS) was defined as the date from randomization to the time of death for those who died of lung cancer or of complications of its treatment, and it was censored at the date of death for those who died of other causes or at the date of the last known follow-up, for patients alive at the time of analysis. Exploratory analyses were performed to characterize the relationship between age and CCIS with baseline characteristics and outcomes, including age, sex, race/ethnicity, performance status (PS), histology, stage, hemoglobin, alkaline phosphatase, time from diagnosis to random assignment, and chemotherapy (type, total dose, survival, and tumor response).

The following factors were assessed in both univariate and multivariant analyses for their influence on survival (OS, PFS, and DFS): age (< 65 years $v \geq 65$ years), CCIS (0 v 1 v 2+), sex, race/ethnicity (white v others), PS (0 v 1 v 2+), hemoglobin (≥ 120 $v < 120$ g/dL), alkaline phosphatase (normal v increased), and time from diagnosis to random assignment (< 6 $v \geq 6$ months). The Cochran-Mantel-Haenszel χ^2 test was used to assess associations between categorical variables; Kaplan-Meier curves were used to estimate the distributions of time to event outcomes; and the Cox regression model stratified by assigned treatment and by disease stage was used to correlate age, CCIS groups, and other baseline factors with the time to event outcomes (OS, PFS, and DSS). The logistic regression model was used to study the effects of age and CCIS on response and toxicity while adjusting for other important prognostic factors. Statistical analyses were carried out using SAS version 8.1 (SAS Institute, Cary, NC). All reported P values are two-sided unless otherwise specified.

RESULTS

A total of 1,255 patients were included in this analysis; 481 (38%) were enrolled onto JBR 10, and 774 (62%) were enrolled onto BR 18. One patient was excluded from the analysis because of missing baseline data. The median age was 61 years (range, 34 to 89 years), and 34% were 65 years or older. Elderly patients were more likely than nonelderly to have a PS of ≥ 1 ($P = .007$), squamous histology (34% v 26%; $P = .005$), time from diagnosis to random assignment of more than 6 months (13% v 5%; $P < .0001$), and comorbid conditions (42% v 26%; $P < .0001$; Table 1). As listed in Table 1, 31% of patients had comorbid conditions in addition to NSCLC; 310 had a CCIS of 1; and 81 had CCIS of ≥ 2. A greater CCIS was associated with male sex (35% v 21%; $P < .0001$), a worse PS ($P = .003$), nonadenocarcinoma histology ($P = .001$), and a time from diagnosis to random assignment of more than 6 months ($P = .004$). Comparison between covariates was performed, and there was no evidence of interaction.

Treatment Delivery and Related Toxicities

Elderly patients received significantly lower median total doses of chemotherapy (paclitaxel 1,680 mg v 1,410.5 mg, $P = .001$; carboplatin 3,283 mg v 2,285 mg, $P < .0001$; cisplatin 610.5 mg v 326 mg, $P < .0001$; vinorelbine 418 mg v 249 mg, $P < .0001$) but not of BMS-275291/placebo (Table 2). Patients with a CCIS of 1 or 2 also received lower median total doses, but the difference was significant only for paclitaxel and carboplatin (Table 3).

Univariate analysis, stratified by the treatment received, showed that elderly patients were more likely to suffer grade 3 or higher toxicities, including gastrointestinal symptoms ($P = .03$), neurologic symptoms ($P < .001$), and fatigue ($P = .01$). Patients with a comorbidity were more likely to have grade 3 or higher gastrointestinal toxicity ($P = .02$), infection ($P = .03$), rash ($P = .01$), or nausea ($P = .01$; Table 4).

Objective Response Rate (BR 18)

Neither age nor comorbidity was predictive of objective response. However, a PS of 0 or 1 ($P = .02$), squamous histology ($P < .001$), stage III disease at diagnosis ($P < .001$), weight loss

Table 1. Baseline Factors by Age Group and by Comorbidity Index Group

Factors	Age Group (%)			Charlson Comorbidity Index			
	< 65 Years	≥ 65 Years	*P*	0	1	≥ 2	*P*
Total participants*				864	310	81	
No.	827	428					
%	66	34		69	25	6	
Sex			NS				< .0001
Male	65	35		65	27	8	
Female	68	32		79	18	3	
Race/ethnicity			NS				.05
White	65	35		68	25	7	
Other	68	32		73	24	4	
ECOG PS			.007				.003
0	70	30		75	19	5	
1	64	36		66	27	7	
2	55	45		58	33	9	
Histology			.005				.001
Squamous	60	40		64	27	8	
Adenocarcinoma	70	30		74	22	4	
Other	65	35		63	27	9	
Hemoglobin, g/L			NS				NS
< 120	66	34		70	24	6	
≥ 120	66	34		69	25	7	
Time from diagnosis to random assignment, months			< .0001				.004
< 6	68	32		70	25	6	
≥ 6	45	55		59	27	14	
Alkaline phosphatase			NS				NS
Normal	66	34		70	24	6	
Increased	67	33		64	29	7	

Abbreviations: NS, not significant; ECOG PS, Eastern Cooperative Oncology Group performance status.
*Median age, 61 years (range, 34 to 89 years) for all patients studied.

less than 5% ($P = .05$), and a serum albumin level greater than 35 g/L ($P = .004$) were significantly associated with a higher response rate. In multivariate analyses, PS ($P = .01$), histology ($P < .001$), stage ($P = .002$), and normal albumin ($P = .02$) remained significant.

Survival

In univariate analyses, age was not prognostic (hazard ratio [HR], 1.03; $P = .72$; Fig 1), but a CCIS ≥1 was associated with shorter survival (overall $P = .01$ [CCIS = 1 *v* CCIS ≥ 2]; CCIS = 1: HR, 1.28; 95% CI, 1.09 to 1.5; $P = .003$ [CCIS = 1 *v* CCIS = 0]; CCIS ≥ 2: HR, 1.09; 95% CI, 0.83 to 1.44; $P = .52$ [CCIS ≥ 2 *v* CCIS = 0]; Fig 2). Other poor prognostic factors included PS, male sex, increased alkaline phosphatase, and anemia (Table 5). In multivariate Cox regression models that were stratified by assigned treatment and disease stage, age was not prognostic, but a CCIS of 1 was associated significantly with shorter survival ($P = .03$; Table 5). Neither age nor comorbidity was significantly associated with PFS in univariate or in multivariate analyses.

In univariate analysis, a trend suggested that a CCIS ≥ 1 was associated with shorter DSS ($P = .06$) but that age was not ($P = .68$). In the multivariate analysis, neither CCI nor age was significantly associated with DSS. Other baseline factors associated with shorter DSS were PS, anemia, elevated serum alkaline phosphatase, and male sex.

Table 2. Median Cumulative Treatment Received by Age Group

Treatment (mg)	Age Group (years)		*P*
	< 65	≥ 65	
BMS-275291/placebo	99,600	76,200	.19
Paclitaxel	1,680	1,410.5	.001
Carboplatin	3,283	2,285	< .0001
Cisplatin	610.5	326	< .0001
Vinorelbine	418.1	248.5	< .0001

Table 3. Median Cumulative Treatment Received by CCIS

Treatment (mg)	CCIS			*P*
	0	1	> 1	
BMS-275291/placebo	100,800	75,600	58,200	.12
Paclitaxel	1,680	1,410	1,316	.04
Carboplatin	3,060	2,512.3	2,011	.02
Cisplatin	588	462	368	.51
Vinorelbine	384	318	391	.36

Abbreviation: CCIS, Charlson Comorbidity Index score.

Table 4. Summary of Adverse Events by Univariate Analysis

Adverse Event*	Association by Univariate Analysis			
	With Age ≥ 65 Years	*P*	With Comorbidity	*P*
Cardiovascular	Yes	.09	Yes	.06
GI	Yes	.03	Yes	.02
Infection	No		Yes	.03
Neurology	Yes	< .001	No	
Pain	No		No	
Rash	No		Yes	.01
Vomiting	No		No	
Nausea	No		Yes	.01
Stomatitis	No		No	
Fatigue	Yes	.01	No	

*Grades 3 through 5.

DISCUSSION

Although NSCLC is largely a disease of the elderly, significant disparities exist in the delivery of chemotherapy[24,25] and in clinical trial participation[26] for elderly patients, partly because of fears of unacceptable toxicity related to comorbid conditions.[24] The impacts of age and comorbid conditions on efficacy and toxicity outcomes of standard chemotherapy regimens are important considerations in clinical practice and in clinical trial design.

In this retrospective analysis of more than 1,200 patients, we confirmed a relationship between age and comorbidity. Both age and comorbidity were associated with more severe toxicity and with lower chemotherapy dose intensity. This effect was more pronounced for age in the metastatic trial (BR 18), which suggests that patients in the adjuvant trial (JBR 10) may have been carefully selected. To be eligible for JBR 10, patients needed to be surgical candidates, which likely precluded patients with a serious comorbidity, such as cardiac disease. Comorbidity, but not age, was prognostic and was associated with poorer OS. This prognostic effect seemed more pronounced for a CCIS of 1, but this observation may be confounded by the selected clinical trial population that contained few patients with a CCIS greater than 1. Interestingly, efficacy outcomes were similar in the elderly compared with younger patients, despite lower apparent chemotherapy dose intensity and higher toxicity, which suggests the lack of a clear dose-response effect of chemotherapy used for NSCLC.[27] Alternatively, elderly patients may have less aggressive disease or may have age-related decreases in drug clearance that provide a higher-than-anticipated exposure.[28]

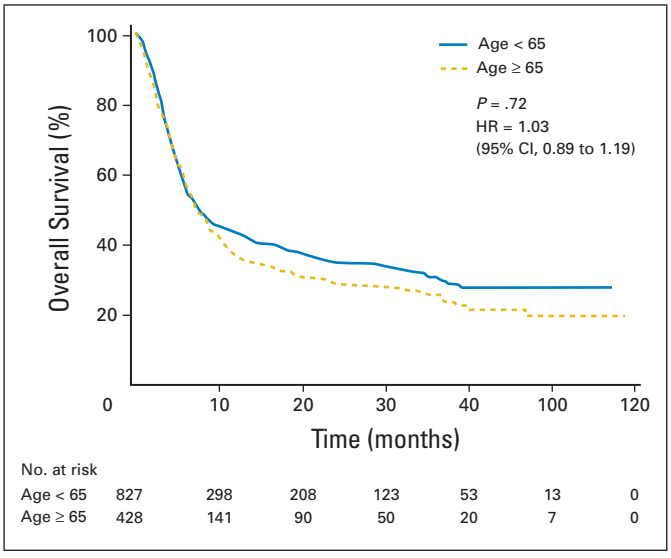

Fig 1. Overall survival by age. HR, hazard ratio.

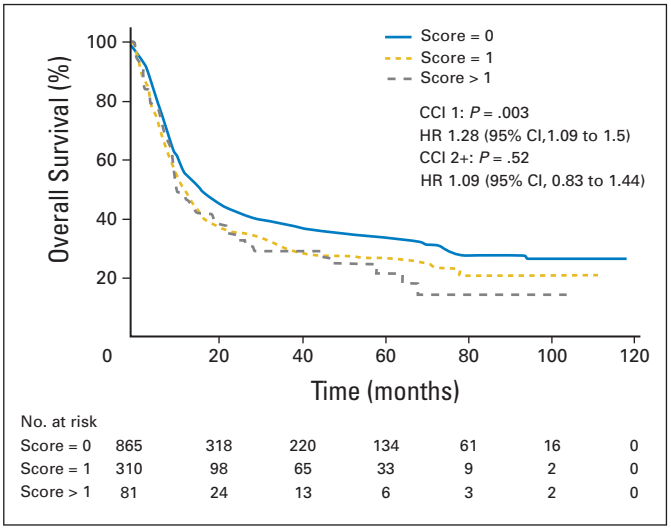

Fig 2. Overall survival by Charlson comorbidity index (CCI) score. HR, hazard ratio.

Our analysis resulted in several observations that are hypothesis-generating and warrant further research. Male sex was associated with a higher CCIS, but adenocarcinomas were associated with a lower CCIS. These results are similar to those reported by Colinet et al,[29] who used a simplified comorbidity score, although age was prognostic in their study, whereas in ours it was not. Poorer outcomes in males is a common observation in NSCLC clinical trials,[30] and our study suggests that this may be accounted for in part by increased comorbidity. The role that sex-dependent hormone pathways might play is as yet not fully understood.[31] The observed relationship among age, CCIS, and histological subtype may be related to tobacco use, as squamous carcinoma is most closely associated with dose and duration of exposure to tobacco. Younger patients may have a shorter exposure to tobacco and may have exposure to a changing tobacco content of cigarettes, so they may be less likely to have comorbidity and more likely to have adenocarcinoma.[32]

Our study was limited in several respects, because this was a retrospective analysis and because both studies excluded patients with poor PS or with significant comorbid conditions, although PS and the CCIS may not be directly correlated.[33] Our study population also had a relatively young median age and therefore may not be representative of the larger NSCLC population. Furthermore, the CCI was not designed specifically for patients with neoplastic disease, and scales designed specifically for cancer patients may be more applicable. Various authors have reviewed comorbidity scales that have been validated in the elderly,[19,34] but further work is necessary to develop a validated, oncology-specific comorbidity scale.

In conclusion, although elderly patients who met the entry criteria for these trials received less chemotherapy, they appeared

Table 5. Univariate and Multivariate Analysis for Overall Survival

Factors	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	Log-Rank *P*	Hazard Ratio	95% CI	Log-Rank *P*
Age group, years			.72			.72
≥ 65	1.03	0.89 to 1.19		0.97	0.84 to 1.13	
< 65	1					
Cumulative comorbidity score			.01			
≥ 2	1.09	0.83 to 1.44				
1	1.28	1.09 to 1.50	.52	0.96	0.72 to 1.23	.75
0	1		.003	1.21	1.02 to 1.42	.03
Sex			.003			.004
Male	1.27	1.08 to 1.48		1.27	1.08 to 1.49	
Female	1					
Race/ethnicity			.52			
White	1					
Other	0.92	0.73 to 1.18			Not in multivariate	
ECOG PS			< .0001			
2	2.45	1.89 to 3.17	< .0001	2.24	1.70 to 2.95	< .0001
1	1.28	1.10 to 1.49	.002	1.25	1.06 to 1.46	.006
0	1					
Hemoglobin, g/L			.0007			.006
≥ 12	1					
< 12	1.35	1.14 to 1.61		1.30	1.08 to 1.56	
Alkaline phosphatase			.0009			.007
Normal	1					
Increased	1.32	1.12 to 1.55		1.25	1.06 to 1.48	
Histology			.77			
Others						
Squamous	1.02	0.87 to 1.20			Not in multivariate	

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

to derive the same benefit as younger patients in terms of OS. Based on our findings and on those of others,[9-12] elderly patients should not be denied access to clinical trials nor to effective therapies on the basis of age alone. In contrast, the presence of comorbid disease was prognostic in this retrospective study and may be a more relevant selection or exclusion criterion for treatment than chronologic age. Further prospective studies should be conducted to examine the relationship among age, comorbidity, and treatment outcomes such as efficacy and toxicity to better tailor therapy for individual patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).