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Low Elderly Participation in Non-Small Cell Lung Cancer Clinical Trials

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Abstract

Background: Lung cancer, with a median age at diagnosis of 70 years, is the current leading cause of cancer mortality in the United States. A lack of elderly enrollment in lung cancer clinical trials, however, has led to difficulty establishing elderly guidelines for treatment and has been highlighted by the Institute of Medicine and the American Society of Clinical Oncology as a key area for improvement. While there have been few elderly-specific clinical trials investigating chemoradiotherapy in lung cancer, there have been no elderly-specific trials investigating targeted therapy or immunotherapy and little is known about elderly outcomes with these agents.

Methods: PubMed was queried for phase I clinical trials involving non-small cell lung cancer (NSCLC) in English in the past five years. Of these 192 studies, 49 investigated targeted therapy and/or immunotherapy without protocolized chemoradiotherapy. These articles were reviewed and assessed based on age demographics and outcomes.

Results: Twelve percent of studies had a mean/median age of 65-69 years; no studies had a mean/median age of 70 years or greater. Of the seven studies with published information on age distribution, only four had information regarding the percentage of participants 70 years or older, which ranged from 8-33% and was limited by a total sample size of 15-26. The few studies that published information on age-specific outcomes suggested that targeted therapy and immunotherapy in the elderly may be as well tolerated and have similar treatment outcomes, but were limited by the small number of elderly participants in these trials.

Conclusion: Additional research involving elderly enrollment and outcomes in NSCLC clinical trials is warranted. Increased recruitment of the elderly in clinical trials and publication of elderly-specific outcomes in lung cancer research is key to improving treatment guidelines in this field.

Keywords: Elderly; Non-small cell lung cancer; Clinical trial; Targeted therapy; Immunotherapy

Introduction

Cancer in the aging population has attracted increasing attention in the United States related both to the growing percentage of individuals over the age of 65 years as well as the increased vulnerability of this aging population to morbidity and mortality [1-4]. Lung cancer, of which non-small cell lung cancer (NSCLC) comprises 85% [5], is an area of particular interest. Two-thirds of all new cases of lung cancer are diagnosed in those 65 years or older [5], but elucidation of elderly-specific NSCLC guidelines has been problematic [6,7]. There simply is not enough data on the treatment of elderly NSCLC patients to form comprehensive evidence-based recommendations. This situation is not unique to NSCLC, and both the Institute of Medicine (IoM) and American Society of Clinical Oncology (ASCO) have issued position statements urging cancer researchers to improve the evidence for treating older adults [1,2].

ASCO, in a position statement published online ahead of print July 2015, identified inclusion of elderly patients in clinical trials a key point of action [2]. Patients over the age of 70 have previously accounted for only 10% of participation in clinical trials [8], and although more recent data has suggested this may be improving, overall enrollment of the elderly in clinical trials and NSCLC clinical trials has continued to be unrepresentative [9-11]. Potential reasons for suboptimal clinical trial recruitment and enrollment are varied, including perceived toxicity risk, increased comorbidities, difficulty with functional assessment, concerns regarding physiologic changes with senescence, socioeconomic and financial disparities, and age bias on the part of researchers, patients, and their families [1]; yet there have been no findings to support an age limit to the benefits of treatment [6]. A 2005 review of chemoradiotherapy NSCLC trials supported the elderly suffer low rates of severe adverse events with no statistically significant differences in survival compared to their younger peers [12]. Nevertheless, targeted therapy and immunotherapy, agents of considerable interest in current NSCLC treatment, remain an area of uncertainty for elderly patients [7,13]. As of July 2015, there had been no elderly-specific trials with targeted therapy, immunotherapy, or a combination of these therapies with chemotherapy or radiation and few elderly-specific outcomes published in large, prospective, randomized trials with these agents.

Methods

The PubMed database was queried for Medical Subject Headings (MeSH) including NSCLC/therapy and “Phase I” or “Phase 1”. Limits

were set to clinical trials in English in the past 5 years with human subjects. A total of 192 studies met these criteria, which were further limited to 155 based on exclusion of descriptive, retrospective, mislabeled and observational/characterization studies, as well as those not directly related to treatment of NSCLC. Of these studies, 49 included treatment with targeted therapy or immunotherapy without protocolized chemoradiotherapy (see Appendix). These studies were assessed based on target population, intervention, sample size, age demographics, and outcomes, including grade 3-4 toxicities. When available, information on treatment completion (TC), overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) were included as well as any differences in patients 70 years and above (elderly) and 85 years and above (extreme elderly).

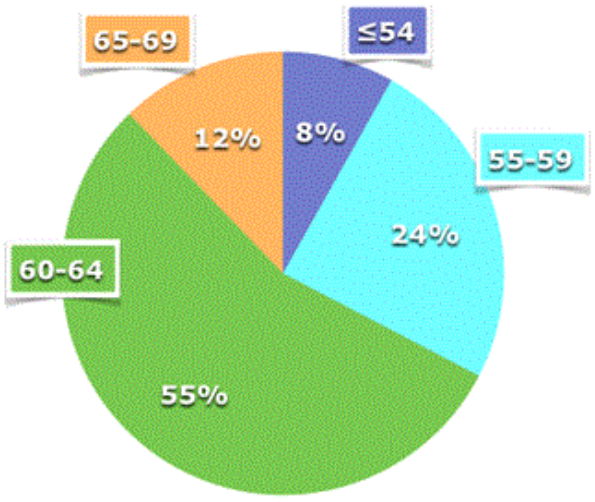

Figure 1: Distribution of Mean/Median ages (in years).

Results

Approximately two-thirds of the studies meeting inclusion criteria involved advanced NSCLC; the remaining studies evaluated two or more solid malignancies. Targeted therapy was the focus of 70% of the studies, 24% involved immunotherapy, 6% involved other agents. Sample size ranged from 5-495 participants: 28% had less than 20 participants, 38% had 20-49 participants, 16% had 50-99 participants, and 18% had over 100 participants. The mean/median age ranged from 46-69 years. Twelve percent of the trials had mean/median ages 65-69 years, 54% 60-64 years, 24% 55-59 years, and 8% less than 54 years (Figure 1).

Seven studies included sufficient information to calculate a percentage of participants above the age of 70 years, which ranged from 8-33% (Table 1). Percentages >17 were in studies with 15 participants or less. Three additional studies provided information regarding the percentage of participants over the age of 60 and 65 years (Table 1). Twenty percent of trials had at least one patient over the age of 85 years, 12% 80-84 years, 43% 75-79 years, 10% 70-74 years; 8% had participants younger than 70 years (Figure 2) [14,15].

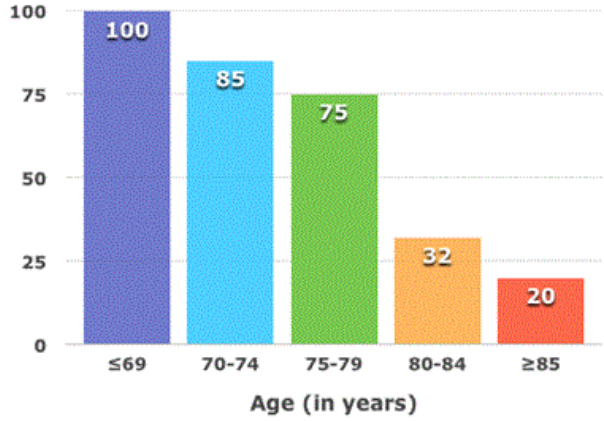

Figure 2: Percentage of Studies including atleast one participant in each age category.

Six percent of studies did not publish this information. Only three studies had age limits to enrollment at 70, 74, and 75 years; these were all published prior to 2012. The maximum age of an enrolled participant was 94 years [16]; Garon [16] included a 93 year-old [17]. Of the ten studies that included a participant 85 years or older, four were immunotherapy studies, six targeted therapy studies, and one other - kahalide F. Of the participants over the age of 70 years with published gender, seven out of nine were men.

Lead author, Year,	Population	Intervention	Sample size	Meant age (y)	Max age (y)	≥70 y* (%)	≥85 y (%)
Wheler [14] 2013	NSCLC stage III-IV	Cetuximab with Eriotinib	20	66	82	NA (≥60 y:60)	0
Suzuki 2013	NSCLC stage III-IV	Peptide Vaccines VEGFR ½, URLC10, TTK protein kinase	15	58	69	NA (≥65 y:27)	0
Camidge 2012	NSCLC stage III-IV w/ALK mutation	Crizotinib	143	52	86	NA (≥65 y:14)	NA$, >1
Brunsvig 2011	NSCLC stage IIIA-IV	Telomearse peptide Vaccination	26	58.5	76	8	0
Sakamoto 2011	Advanced NSCLC	Zoledronate-expanded ¥δ T-cells	15	67	85	33	7 (all male)
Iliopoulou 2010	NSCLC stage IIIB-IV	Allogeneic natural killer cells	15	65	75	20	0

Um 2010	NSCLC stage III-IV	Dendritic cell vaccine	15	60	75	13	0

*Listed chronologically. tWhen mean age is not available, median age is substituted as denoted by whole number without decimal point. 'If information is available for an age set other than ≥70 years, it is designated NA with the appropriate age set and corresponding percentage in parentheses. All values expressed as percentages rounded to the nearest percentage. $Specific percentage not published, but given the Max age of trial, it was determined to be >1. All values expressed as percentages rounded to the nearest percentage.

Table 1: Percentages of Elderly Patients in Targeted therapy, Immunotherapy NSCLC Phase I Clinical trials.

Lead author, year	Design'	Sample characteristics'	Intervention	Sample size	Mean• age (y)	Max age (y)	≥70 y	Outcomes	Elderly Outcomes'
Sukzuki 2013	Single center, open-label, single arm	NSCLC stage III-IV, age≥20, PS 0-2, HLA-24 positive Exclusion: autoimmune disease, systemic steroid use	Peptide vaccines VEGFR1/2, URLC10, TTK protein kinase; weekly injections	15	58	69	0≥65 y:4	PFS 2.8 m, OS 13.3 m, 1 y survival 58%, 2Y 33% SD 47%	SD 50% (T-cell responders), PD 50% (minimal responders)
Camidge 2012	Multicenter, open-label, single arm	NSCLC stage III-IV w/ALK mutation, age ≥18, PS 0-2 Exclusion: CNS involvement unless treated/stable>2 wks, prolonged QT	Crizotinib 250 mg po BID 28-day cycle	143	52	86	NA≥65y: 20	PFS 9.7 m 1 y survival 75% OOR 61%	OOR 65%
Takahashi 2012	Single center, open-label, dose escalation 3+3	Advanced solid tumors, age≥20 and ≤75, PS 0-1 Exclusion: CNS metastases, corneal abnormalities	Dacomitinib 15/30/45 mg po daily 21-day cycles	13	63.2	71	NA	PR 8%, SD 69% NSCLC DC 50%	NSCLC DC 80%
Brunsvig 2011	Single center, open-label, dose escalation two cohorts	NSCLC stage IIIA-IV, age ≥18 and ≤75, PS 0-1 Exclusion: HIV, HBV, autoimmune disease, systemic steroid use	Vaccination 112 µg HR2822 and GM-CSF; 3 injections weekly 2,3,4,6,10 w/ booster week 14,18,22, month 6,9	26	57.8	76	2	At 8 years: ORR 31% TC 54%	At 8 Years: ORR 0%, TC 100% (Immune responder OS 19 m, non 3.5 m)
Sakamoto 2011	Single center, open-label, single arm	NSCLC stage III-IV, age≥20, PS 0-2, γδ T-cells 100XD10 vs D1 culture Exclusion: anti-adult T-cell leukemia-associated antigen positivity, HIV, autoimmune disease, systemic steroid use	Expanded γδ T-cells IV biweekly for 6 infusions	15	67	85	5≥85 y:1	PFS 4.2 m, OS 19.6 m SD 40% Toxicities: Increased GGT 7% Lung infection 7% Pneumonitis 7%	SD 40% Toxicities: GGT increased 0% Ling infection 20% Pneumonitis 0%

Abbreviations: CR w complete response. DC w disease control (CR+PR+SD). NA not available. ORR w overall response rate (CR+PR). OS w overall survival. PD w progressive disease. PFS w median progression-free survival. PR - partial response. PS • ECOG Performance Status. SO • stable disease. TC - treatment con:pleb:in rate. 'All trials are prospective, phase I trials published in English in the past 5 years (7/14/2010-7/15/2015). 'List is not exhaustive and includes most pertinent inclusion and exclusion criteria. It should be assumed included patients have measurable disease, are not pregnant or breastieeding, have not had recent treatment with other agents, do not have severe active infections or severe oo-moroid conditions including cardiac, hepatic, or renal disease, have adequate organ function, have no known allergies to the study drug(s), and have the ability to absorb any oral medication without limitations. When mean age is not available, median age is substituted as denoted by whole nurnber without decimal point. !Refers to number of participants over age of 70 years. When ittmiation is available for an age range other than 70 years and older, it is listed with the age range followed by a colon. All values expressed as percentages rounded to the nearest percentage.iDenotes outcomes related to those 65 years and older.

Table 2: Targeted therapy, immunotherapy phase I Non-small cell lung cancer (NSCLC) clinical trials including elderly outcomes.

The only studies that provided sufficient information to correlate outcomes with age included Suzuki, Camidge, Takahashi, Brunsvig, and Sakamoto (Table 2). Three of these studies evaluated immunotherapy. All studies except for Camidge included 26 patients or less. Camidge found that crizotinib in ALK rearranged NSCLC had similar ORR for all patients and those over the age of 65 years (61% vs. 65%, respectively). Suzuki showed that peptide vaccines resulted in similar SD in all patients and those over the age of 65 years (47% vs

50%). Takahashi suggested improved outcomes with dacomitinib for disease control in those over the age of 65 years (80% vs 50%), but was limited by a sample size of 13. Brunsvig found that elderly patients completed telomerase peptide vaccination on par with all patients (100% vs 75%), but enrolled only 2 patients over the age of 70. Sakamoto suggested that infusion of in vitro expanded T-cells led to similar rates of SD in those above and below the age 70 years (40% vs 40%) and was similarly well tolerated; one of 5 patients over the age of 70 had an adverse event; a patient over the age of 85 years had no adverse events.

Conclusion

These findings support that elderly participation in phase I targeted therapy and immunotherapy NSCLC clinical trials is unrepresentative. Data regarding elderly outcomes with NSCLC targeted therapy and immunotherapy is severely limited by low elderly participation rates and omission of elderly-specific data publication. This review supports the IoM and ASCO position statements in that elderly participation and data in clinical trials deserves further attention. Increased recruitment of the elderly in clinical trials and publication of elderly-specific outcomes in lung cancer research is key to improving treatment guidelines in this field.

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