Exclusion of Older Patients From Ongoing Clinical Trials for Hematological Malignancies: An Evaluation of the National Institutes of Health Clinical Trial Registry

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Key Words. Clinical trial design • Elderly • Hematological malignancies • Exclusion criteria

ABSTRACT

Introduction. Cancer societies, research cooperatives, and countless publications have urged the development of clinical trials that facilitate the inclusion of older patients and those with comorbidities. We set out to determine the characteristics of currently recruiting clinical trials with hematological patients to assess their inclusion and exclusion of elderly patients.

Methods. The NIH clinical trial registry was searched on July 1, 2013, for currently recruiting phase I, II or III clinical trials with hematological malignancies. Trial characteristics and study objectives were extracted from the registry website.

Results. Although 5% of 1,207 included trials focused exclusively on elderly or unfit patients, 69% explicitly or implicitly excluded older patients. Exclusion based on age was seen in 27% of trials, exclusion based on performance status was seen in 16%, and exclusion based on stringent organ function

restrictions was noted in 51%. One-third of the studies that excluded older patients based on age allowed inclusion of younger patients with poor performance status; 8% did not place any restrictions on organ function. Over time, there was a shift from exclusion based on age (p value for trend $<.001$) toward exclusion based on organ function ($p = .2$). Industry-sponsored studies were least likely to exclude older patients ($p < .001$).

Conclusion. Notably, 27% of currently recruiting clinical trials for hematological malignancies use age-based exclusion criteria. Although physiological reserves diminish with age, the heterogeneity of the elderly population does not legitimize exclusion based on chronological age alone. Investigators should critically review whether sufficient justification exists for every exclusion criterion before incorporating it in trial protocols. *The Oncologist* 2014;19:1069–1075

Implications for Practice: Although physiological reserves diminish with age, the heterogeneity of the elderly population does not legitimize exclusion based on chronological age alone. However, 27% of the clinical trials in this overview still use age-based exclusion criteria. Investigators should critically review whether sufficient justification exists for each exclusion criterion before incorporating it in trial protocols, and if no restrictions apply for a particular aspect, this should also be noted. As a research community, we cannot continue to simply acknowledge the underrepresentation of older patients in clinical trials. We must all participate in taking the necessary steps to enable the delivery of evidence-based, tailor-made, and patient-focused cancer care to our rapidly growing elderly patient population.

INTRODUCTION

Hematological malignancies are frequently diagnosed in older patients. For disease entities such as myelodysplastic syndrome, acute myeloid lymphoma, Non-Hodgkin lymphoma, chronic lymphocytic leukemia, and multiple myeloma, the median age at diagnosis is 65 years or older [1]. With the imminent aging of society [2], hematologists will be faced with increasing numbers of elderly patients with blood cancer.

Historically, older patients and those with comorbidities have been excluded from clinical trials [3]. Among the U.S. Food and Drug Administration-approved treatments for cancer, only 9% of patients enrolled in registration trials were older than 75 years of age, whereas 31% of patients with cancer are within that age group [4]. Due to differences in physiological reserves, comorbidity, functional capacity, and geriatric syndromes, elderly patients represent a

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Figure 1. Search results and trial selection.

heterogeneous population [5]. These factors may influence the ability of a patient to tolerate treatment and may alter clinical outcome, for instance, by forming competing causes of death. Consequently, it is incorrect to assume that those treatment regimens that are most beneficial for younger patients will also be the best choices for older patients. Moreover, elderly patients that are included in trials may not be representative of the population in daily clinical practice [6].

Since the end of the 20th century, cancer societies, research cooperative groups worldwide, and countless publications have addressed the underrepresentation of older patients in trials and urged the development of clinical trials that will facilitate or at least allow the inclusion of older patients and those with comorbidities [3, 7–9]. Fifteen years onward, many questions remain unanswered. There are still no adequate data on which to base treatment choice, adjust dosing, or anticipate possible side effects for elderly patients [7]. Given the time that transpires between the first conceptualization of a study and the publication of final results, any progress in the next 10 years is most likely to come from clinical trials that are currently ongoing. However, this is possible only if these trials include sufficient numbers of older patients that are representative of the general older population. To evaluate this question, we set out to determine the characteristics of currently recruiting clinical trials with hematological patients.

METHODS

To identify ongoing phase I, II, or III clinical trials focused on hematological malignancies, the NIH clinical trial registry (<http://www.clinicaltrials.gov>) was searched on July 1, 2013, using the search terms “cancer” and “hematological neoplasm.” The search was limited to interventional phase I, II, and III trials or mixed phase I/II or II/III trials currently recruiting patients or intending to start recruitment within the next 6 months; trials with unknown recruitment status or without any verification of this status in the last 12 months were excluded.

For included trials, the following data were extracted from the registry website: target disease entities; source of funding; type of intervention; and inclusion and exclusion criteria with particular focus on age limits, comorbidity, organ function, and performance status (PS). Restrictions regarding organ function and comorbidity were classified into the following categories: “hepatic,” “renal,” “bone marrow,” “pulmonary,” “cardiac,” “other cardiovascular disease,” “prior oncologic history,” and “psychiatric history.” For each category, restrictions were

labeled as “moderate” or “strict” or as “none” if no exclusion criteria pertaining to that category were mentioned. This classification was previously used by Lewis et al. [10], and full details by category can be found in the supplemental online data. Briefly, strict exclusions were those protocol exclusion criteria that required normal or nearly normal laboratory values or organ function, whereas moderate exclusions allowed for mildly abnormal values while still imposing some restrictions.

To allow combining of data on performance status, a Karnofsky PS of 100 was considered equivalent to a World Health Organization (WHO) PS of 0, Karnofsky PS 80–90 was considered equivalent to WHO PS 1, Karnofsky 60–70 was considered equivalent to WHO PS 2, Karnofsky 40–50 was considered equivalent to WHO PS 3, and Karnofsky PS ≤ 30 was considered equivalent to WHO PS 4 [11].

Trials were considered to be excluding elderly patients based on age if they used an upper age limit of 75 years or younger; exclusion based on performance status was recorded for trials that allowed inclusion only of the very fit (WHO PS 0–1), and exclusion based on organ function was noted if they used one stringent organ function restriction or more.

Statistical Analyses

SPSS version 21.0 (IBM Corp., Armonk, NY, <http://www-01.ibm.com/software/analytics/spss/>) was used for the analyses. To assess differences between categories, the chi-square test was used, or a trend test (linear-by-linear) was used when levels were ordered. A p value of $<.05$ was considered statistically significant.

RESULTS

A total of 39,376 trials were identified in the trial registry search (Fig. 1), of which 1,207 were included in this overview. Characteristics of selected trials are listed in Table 1. The trials covered a wide variety of diagnoses, with the most frequent being multiple myeloma (16%), acute myeloid leukemia (11%), and non-Hodgkin lymphoma (10%). Almost all trials included some form of chemotherapy (96%), with 43% using biologicals and 8% involving hematopoietic stem cell transplantation. Phase II trials composed 43% of included trials, 25% were phase I trials, 19% were combined phases I and II, 1% were combined phases II and III, and 12% were phase III trials. Overall, 47% of trials were industry-sponsored.

Most trials had a lower age limit for inclusion of younger than 21 years (94%) (Table 1). Only 62 trials (5%) excluded patients aged younger than 60 years, focusing specifically on older patients; 91% of these trials were initiated in the past 4

Table 1. Characteristics of selected trials

Trial characteristic	n	%
Diagnosis		
Multiple hematological malignancies	451	37
Acute lymphocytic leukemia	49	4
Acute myeloid leukemia	135	11
Chronic lymphocytic leukemia	81	7
Chronic myeloid leukemia	46	4
Multiple myeloma	196	16
Myelodysplastic syndrome	64	5
Non-Hodgkin lymphoma	122	10
Hodgkin lymphoma	36	3
Other diagnoses	27	2
Start year		
≤2005	34	3
2006–2007	54	5
2008–2009	140	12
2010–2011	395	33
2012–2013	584	48
Intervention^a		
Chemotherapy	1,161	96
Biologicals	514	43
HSCT	98	8
Other interventions	41	4
Phase		
I	307	25
I/II	227	19
II	513	43
II/III	13	1
III	147	12
Sponsor^a		
Industry	568	47
National Institutes of Health	227	15
Other	816	68

^aTrials could have multiple interventions and multiple sponsors. Abbreviation: HSCT, hematopoietic stem cell transplantation.

years. Two-thirds of trials did not state an upper age limit; 5% had an upper age limit of younger than 50 years of age, 10% had an upper age limit between 51 and 69 years, 13% had an upper age limit between 70 and 79 years, and 4% had an upper age limit of 80 years or older. Almost all trials allowed inclusion of patients with WHO PS 0 or 1, 16% excluded patients with WHO PS 2, and 73% excluded WHO PS 3. Eight trials (0.6%) included patients with only WHO PS 2 or higher.

More than 92% of trials placed some restriction on organ function in the inclusion and exclusion criteria (Table 2), and 51% formulated one stringent restriction or more. Hepatic function (77%) and renal function (74%) were most frequently included, with 33% and 21% of trials, respectively, placing stringent restrictions. Cardiac function was also commonly included (68% overall, 19% stringent), and 12% of trials also placed restrictions with regard to other cardiovascular disease, of which 3% were stringent restrictions. Less frequently

mentioned were bone marrow function (39%) and pulmonary function (26%), of which 1% and 2% of trials, respectively, formulated stringent restrictions. One-third of trials placed restrictions on prior oncological history, with 2% excluding patients with any prior malignancy, and 24% limited inclusion of patients with prior or current psychiatric illness.

Overall, 827 trials (69%) explicitly or implicitly excluded elderly patients: 12% were based only on an upper age limit, 4% were based only on restrictions with regard to performance status, 31% were based only on strict organ function restrictions, and the remaining 23% were based on a combination of restrictions (age and PS, 3%; age and organ function, 11%; PS and organ function, 5%; age, PS, and organ function, 4%). Of trials excluding elderly patients based on age, 35% allowed inclusion of younger patients with WHO PS 3 and 23% allowed inclusion of younger patients with WHO PS 4. Furthermore, 8% of these trials did not place any restrictions with regard to organ function for younger patients, 19% placed no restrictions on hepatic function, 22% did not formulate restrictions for renal function, 25% had no restrictions on cardiac function, 54% had no restrictions on pulmonary function, and 76% did not have any requirements with regard to bone marrow function.

Tables 3 and 4 show the proportion of trials explicitly or implicitly excluding older patients on the basis of age, performance status, and organ function restrictions, analyzed separately for disease entities and other trial characteristics. Trials focusing on acute lymphocytic leukemia and those focusing on some form of hematopoietic stem cell transplantation were most likely to exclude older patients (88% and 90% of trials, respectively) (Table 3); these trials were also most likely to base exclusion on age itself (67% and 75%, respectively). Trials for patients with chronic lymphocytic leukemia were least likely to exclude older patients (56%) and infrequently used age as an exclusion criterion (6%). Industry-sponsored trials were least likely to exclude older patients (60% of trials compared with 80% of trials sponsored by the NIH and 72% of trials with other sponsors; $p < .001$) (Table 4) and were also least likely to exclude patients based on age itself (14% compared with 30% and 34% of trials sponsored by the NIH and other sponsors, respectively; $p < .001$).

Over time, there was a slight trend toward less exclusion of elderly patients, although this was not statistically significant ($p = .21$) (Fig. 2); however, there was a decrease in exclusion based on age itself ($p < .001$) and an increase in exclusion due to restrictions placed on organ function ($p = .02$).

DISCUSSION

In this overview of hematological phase I–III trials registered in the NIH clinical trials registry, we found that 5% focused exclusively on elderly or unfit patients, whereas 69% of trials explicitly or implicitly excluded older patients. Exclusion based on age was seen in 27% of trials, exclusion based on performance status was seen in 16%, and exclusion based on stringent organ function restrictions was noted in 51%. One-third of studies that excluded older patients based on age allowed inclusion of younger patients with poor performance status, and 8% did not place any restrictions on organ function. Over time, there was a shift from exclusion based on age toward exclusion based on organ function. We also found that

Table 2. Inclusion and exclusion criteria of selected trials

Criteria	n	%
Lower age limit, years		
<21	1,129	94
22–59	16	1
60–64	43	4
65–69	15	1
≥70	4	0
Upper age limit, years		
None	830	69
<50	66	5
51–64	45	4
65–69	73	6
70–74	73	6
75–79	78	7
80–84	302	3
85–90	10	1
PS ^a		
PS 0 excluded	9	1
PS 1 excluded	8	1
PS 2 excluded	195	16
PS 3 excluded	879	73
PS 4 excluded	977	81
Organ system restrictions		
Bone marrow function ^b		
No restrictions	734	61
Moderate restrictions	466	39
Stringent restrictions	7	1
Hepatic function ^b		
No restrictions	275	23
Moderate restrictions	531	44
Stringent restrictions	401	33
Renal function ^b		
No restrictions	309	26
Moderate restrictions	645	53
Stringent restrictions	253	21
Pulmonary function ^b		
No restrictions	887	74
Moderate restrictions	294	24
Stringent restrictions	26	2
Cardiac function ^b		
No restrictions	390	32
Moderate restrictions	588	49
Stringent restrictions	229	19
Other cardiovascular disease (i.e., hypertension, thromboembolic or cerebrovascular events) ^b		
No restrictions	1,052	87
Moderate restrictions	114	9
Stringent restrictions	41	3
Prior oncological history ^b		
No restrictions	825	68
Moderate restrictions	354	29
Stringent restrictions	28	2

Table 2. (continued)

Criteria	n	%
Psychiatric history ^b		
No restrictions	925	77
Moderate restrictions	272	23
Stringent restrictions	10	1

Trials were considered to be excluding elderly patients based on age if they used an upper age limit of 75 years or younger, based on PS if they allowed inclusion only of the patients with PS 0–1, and based on organ function if they used one stringent organ function restriction or more. Multiple restrictions per trial were possible.

^aKarnofsky PS 100 was considered equivalent to World Health Organization (WHO) PS 0, Karnofsky PS 80–90 was considered equivalent to WHO PS 1, Karnofsky PS 60–70 was considered equivalent to WHO PS 2, Karnofsky PS 40–50 was considered equivalent to WHO PS 3, and Karnofsky PS ≤30 was considered equivalent to WHO PS 4 [11].

^bClassification of organ function is in accordance with Lewis et al. [10]. Details can be found in the supplemental online data. Abbreviation: PS, performance status.

industry-sponsored studies were least likely to exclude older patients.

This study has several limitations. First, we focused exclusively on the NIH clinical trials registry; therefore, we do not have full representation of all clinical trials worldwide. However, the NIH clinical trials registry is by far the largest; in comparison, a search of the second largest registry (the European Union clinical trials registry, <http://www.clinicaltrialregister.eu>) using the same search terms yielded only 4,200 trials, nearly one-tenth the number included in this overview. A second limitation is that there is no consensus on which cut-off values represent strict or moderate restrictions in organ function, and each cutoff can be open to debate. To circumvent this issue, we chose to use a classification method that was previously used in a peer-reviewed and often cited publication by Lewis et al. [10]. Finally, we had access only to the data as reported by the primary investigators on the registry website. It is possible that other inclusion and exclusion criteria were formulated for the study protocol that were not considered of sufficient importance to be mentioned on the registry website.

Some researchers have questioned the desirability of including older patients and those with comorbidity in clinical trials because these patients are less likely than fit, younger patients to benefit from certain therapies and increasing the participation of elderly patients in clinical trials could produce less-conclusive results with smaller treatment effects [10]. However, the clinical applicability of trial results depends largely on whether the study participants are representative of the population of interest [6]. Consequently, for disease entities for which the majority of patients actually are older patients with comorbidities, including these patients will supply a much more faithful reflection of true clinical benefit [12]. Such trials will allow cancer specialists to make treatment recommendations that apply to their real-life patient populations rather than to highly selected subgroups. As demonstrated by Table 3, for at least five types of hematological malignancy, the median age at diagnosis is older than 65 years [1], and trials addressing these diseases should not exclude elderly patients.

Table 3. Exclusion of older patients by diagnosis

Diagnosis	Ongoing clinical trials					SEER data ^a	
	Number of trials	Proportion of trials excluding older patients (%) ^b	Proportion excluding older patients based on age (%) ^b	Proportion excluding older patients based on performance status (%) ^b	Proportion excluding older patients based on organ function (%) ^b	Median age at diagnosis (years)	Patients aged >65 years at diagnosis (%)
Acute lymphocytic leukemia	49	88	67	8	49	14	10.8
Hodgkin lymphoma	36	69	44	17	47	38	17.7
Chronic myeloid leukemia	46	72	22	11	63	64	48.8
Non-Hodgkin lymphoma	122	61	16	17	51	66	54.4
Acute myeloid leukemia	135	78	42	19	49	67	54.1
Multiple myeloma	196	63	19	19	48	69	62.4
Myelodysplastic syndrome	64	67	17	9	56	70	80.0
Chronic lymphocytic leukemia	81	56	6	6	53	71	68.1
Various hematological malignancies	451	70	30	18	51	—	—
Other diagnoses	27	74	19	11	56	—	—

^aThe SEER program collects information on incidence, prevalence, and survival from specific geographic areas representing 28% of the U.S. population.

^bTrials were considered to be excluding elderly patients based on age if they used an upper age limit of 75 years or younger, based on performance status if they allowed inclusion only of the patients with performance status 0–1, and based on organ function if they used one stringent organ function restriction or more. Multiple restrictions per trial were possible.

Abbreviations: —, not applicable; SEER, Surveillance, Epidemiology, and End Results.

Table 4. Exclusion of older patients by trial characteristic

Trial characteristic	Number of trials	Proportion of trials excluding older patients (%) ^a	Proportion excluding older patients based on age (%) ^a	Proportion excluding older patients based on performance status (%) ^a	Proportion excluding older patients based on organ function (%) ^a
Intervention ^b					
Chemotherapy	1,161	64	23	18	46
Biologicals	514	66	22	16	52
HSCT	98	90	75	39	39
Other interventions	41	71	59	27	34
Phase I	307	8	23	15	54
Phase I/II	227	68	27	13	52
Phase II	513	71	29	19	53
Phase II/III	13	77	62	31	31
Phase III	147	60	29	13	39
Sponsor ^b					
Industry	568	60	14	14	40
NIH	227	80	30	17	59
Other	816	72	34	17	53

^aTrials were considered to be excluding elderly patients based on age if they used an upper age limit of 75 years or younger, based on performance status if they allowed inclusion only of the patients with performance status 0–1, and based on organ function if they used one stringent organ function restriction or more. Multiple restrictions per trial were possible.

^bTrials could have multiple interventions and multiple sponsors.

Abbreviation: HSCT, hematopoietic stem cell transplantation.

Previous studies have demonstrated that protocol exclusion criteria based on comorbid conditions or functional status disproportionately disqualify older patients from clinical studies and are a significant factor in the underrepresentation of

elderly patients in trials [10]. However, it is important to emphasize that many exclusion criteria are not arbitrary; oncologic treatments are toxic and thus require the presence of sufficient reserves to weather possible side effects. Poor

Figure 2. Time trends for exclusion of elderly overall, and based on age, performance status and organ function. Chi-square tests were used to determine statistical significance; a p value $< .05$ was considered statistically significant.

performance status and decreased organ function have been demonstrated to be strong predictors of treatment toxicity [13]. Exclusion of patients who are likely to suffer more than gain from a treatment is legitimate; however, it is not unlikely that some exclusion criteria are more or less routinely formulated based on assumptions or prior protocols. We recommend that when designing a clinical trial, investigators should critically examine each exclusion criterion and ascertain whether it is truly necessary and scientifically justifiable for that particular trial before including it in the protocol.

Furthermore, it is generally acknowledged that elderly patients represent a heterogeneous population and that chronological age is not an adequate representation of biological age [14]. Consequently, any exclusion of elderly patients based solely on age is, by definition, arbitrary, particularly if no other limitations are placed on performance status or residual organ function. It is promising to see that, over time, the use of age-based exclusion is diminishing (Fig. 2), and we are hopeful that this trend will continue in the future. Another development that will provide further improvements in the evidence on cancer treatments for elderly patients is the increased number of trials focusing specifically on elderly or unfit patients. This focus allows for the evaluation of less aggressive treatments in patients for whom standard treatment is expected to be too toxic.

Even trials that allow the inclusion of older patients do not always succeed in recruiting adequate numbers. There appears to be an inherent reluctance on the part of physicians to enroll older patients [6], and even if a suitable trial is available, this option is not always offered to elderly patients. One study using a survey of oncologists, for example, found that 50% declared patients unsuitable for clinical trials on the basis of age alone [15], whereas another study demonstrated that only 34% of elderly patients fulfilling eligibility criteria were offered a particular trial compared with 68% of younger patients ($p < .001$) [16]. In contrast, another study demonstrated that it is important to be explicit when no restrictions are applied to a specific aspect such as age, performance status, or residual

organ function. The authors found that in protocols that did not specify criteria regarding performance status, older patients accounted for 16% of participants; by comparison, in protocols that specifically stated that patients with low performance status were eligible, 63% of participants were elderly [17]. Making inclusion more explicit could aid in overcoming the cancer specialist's hesitation in offering a trial. This approach will need to be supplemented with a sustained effort by the research community to educate physicians on the need for and the possibility of enrolling older patients in clinical trials [18–21].

Other barriers to enrollment of older patients exist, such as the fact that older patients may not be as willing to participate in trials, particularly when this will involve random assignment of a treatment regimen, as is often the case in clinical trials [21–24]. However, a study on the attitudes of older patients toward enrollment in clinical trials demonstrates that, despite initial hesitation due to randomization, more than 75% of patients were willing to participate after additional explanation of the trial process [18]. Another study demonstrated that the amount of time spent with the patient (by the treating physician or a clinical research assistant) was identified as an important factor associated with the likelihood of participation of older patients in clinical trials [19]. When designing clinical trials, allocating sufficient time to endorse and explain the trial could significantly contribute to successfully recruiting greater numbers of older patients.

CONCLUSION

Notably, 27% of currently recruiting clinical trials with hematological malignancies still use age-based exclusion criteria. Although physiological reserves diminish with older age, the heterogeneity of the elderly population does not legitimize exclusion based on chronological age alone. Investigators should critically review whether sufficient scientific justification exists for each exclusion criterion before incorporating it in trial protocols, and if no restrictions apply for a particular aspect, this should also be noted. Furthermore, cancer

specialists should endorse trial participation and allocate sufficient time to explain the trial process and the necessity of research to their patients. We cannot continue to simply acknowledge this issue. We must all take the necessary steps to enable the delivery of evidence-based, individually tailored, and patient-focused cancer care to our rapidly growing elderly patient population.

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