Survival for older patients with acute myeloid leukemia: a population-based study

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ABSTRACT

Background
Acute myeloid leukemia is the second most common leukemia among United States adults with a median age of 69 years. We investigated recent clinical practices related to treatments and disease outcomes in older patients with acute myeloid leukemia in the United States.

Design and Methods
In this retrospective cohort study, we used Surveillance, Epidemiology, and End Results program data from 2000 through 2007 linked to Medicare enrollment and utilization data in the United States.

Results
Among 5,480 patients with acute myeloid leukemia (median age 78 years, range 65-93), 38.6% received leukemia therapy within three months of diagnosis (treated group). Practice changed with 16.3% of treated patients receiving hypomethylating agents after 2004 when those agents became available. Median survival was two months in the untreated group *versus* six months in the treated group ($P<0.01$) with the biggest improvements seen in those aged 65-69 years (10 months *vs*. 4 months; $P<0.01$) and 70-74 years (8 months *vs*. 3 months; $P<0.01$). In 46 patients receiving allogeneic hematopoietic cell transplantation (0.8%), the median survival from diagnosis was 22 months.

Conclusions
Therapy for leukemia improves overall survival in older acute myeloid leukemia patients. Based on their comorbidities, most patients up to 80 years of age should be considered for treatment. New therapies including hypomethylating agents and allogeneic hematopoietic cell transplantation are promising and must be compared with other chemotherapy regimens.

Key words: acute myeloid leukemia, older patients, treatment, disease outcome, survival.

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The online version of this article has a Supplementary Appendix.

Introduction

Acute myeloid leukemia (AML) is the second most common type of leukemia among United States (US) adults with an age-adjusted incidence of 3.6 per 100,000 per year and a median age of 69 years at diagnosis.[1] A few population-based studies have reported 3-year survival rates of only 9-10% and 5-year survival of 3-8% in patients aged 60 years and older, compared with 5-year survival rates of up to 50% for younger patients.[2-4] This poor survival reflects the higher frequency in older patients of poor prognostic factors and comorbidities, as well as a preference among physicians not to treat older patients as aggressively because of the expectation that they are less likely to benefit from intensive therapies.[5]

Despite the paucity of clinical studies evaluating different treatment options in older AML patients,[6] there is some evidence available on treatment practices and associated outcomes in older AML patients.[2,7-10] A recent study from the Swedish Acute Leukemia Registry showed that the proportions of patients eligible for intensive treatment depended on age and performance status, and suggested that fit AML patients up to 80 years of age should be considered for intensive therapy.[2] In the US, approximately a decade ago, analysis of data in the Surveillance, Epidemiology, and End Results (SEER) cancer registry and Medicare claims database (SEER-Medicare) (1991-1999) found that 33.8% of AML patients aged 65 years or over received chemotherapy, though the curative or palliative intent of treatment could not be ascertained.[9] Notably, the median survival for all patients in this older age group was only 2.4 months.

During the last decade, new strategies have emerged for treating AML. Specific improvements include the availability of new drug therapies[11-13] and the development of reduced intensity conditioning (RIC) for allogeneic hematopoietic stem cell transplantation (allo-HCT).[14-17] Based on these new treatment approaches, plus improvements in supportive care, we hypothesized that the poor prognosis of older AML patients reported in the 1990s might have improved during the last decade. In the present study, using the SEER-Medicare database, we examined a population-based cohort of older patients in the US diagnosed with AML from 2000-2007, and investigated the use of newer diagnostic testing modalities and compared the effects of different therapeutic interventions on survival rates.

Design and Methods

Data source

After receiving approval from the University of Minnesota Institutional Review Board, we used data from the population-based (SEER) program database and linked Medicare files. Sponsored by the National Cancer Institute (NCI), SEER collects and publishes cancer incidence, treatment, and survival data from population-based cancer registries covering approximately 28% of the US population.[18,19] A 98% case ascertainment is mandated with annual quality-assurance studies.[18] SEER databases are linked to Medicare enrollment and claims files at the individual level to allow tracking of cancer- and non-cancer related medical service utilization by Medicare beneficiaries before and after their cancer diagnosis. The vast majority (93%) of persons aged 65 years and older in SEER are successfully matched to Medicare enrollment files.[20] At the time of our study, the SEER-Medicare linkage included all Medicare-eligible people in the SEER database through 2007, and their Medicare enrollment and claims data through 2009, thus permitting a minimum 2-year follow up.

Study cohort

With the aim of investigating current clinical practice in older *de novo* and secondary AML in the US, patients in the SEER database were included if their first primary cancer diagnosis was AML between 1st January 2000 and 31st December 2007 (*Online Supplementary Figure S1*). This restriction indirectly enabled us to exclude therapy-related AML, since SEER does not code the specific subtype of AML. All patients had microscopically confirmed AML diagnosis based on the World Health Organization (WHO) classification system, including International Classification of Diseases for Oncology (3rd edition, ICD-O-3) histology codes in SEER data (*Online Supplementary Tables S1 and S2*). To ensure complete information, analysis was limited to those likely to have complete claims data. Continuous enrollment in Medicare Part A and Part B with no health maintenance organization (HMO) enrollment was required from 12 months preceding the AML diagnosis that allowed ascertainment of active comorbidities. Patients were excluded if their diagnosis was made through autopsy, death certificate or nursing home records, or if they were diagnosed with another cancer in the two years following their AML diagnosis.

The NCI provides a comprehensive list, the International Classification of Diseases (9th revision), Clinical Modification (ICD-9-CM) of diagnosis and procedure codes, and Healthcare Common Procedure Coding System (HCPCS) "J" codes, which are used to identify claims for chemotherapy.[21-23] The HCPCS codes are for specific drugs, whereas the ICD-9-CM codes indicate only that chemotherapy was provided and do not identify the specific drugs used. We searched the Medicare National Claims History (NCH) and Outpatient files to identify patients who received infused chemotherapy. A course of leukemia therapy was defined as primary therapy if it was delivered within three months of diagnosis. Patients with therapy (treated group) were classified into two groups based on specific drug use: chemotherapy or hypomethylating agents (5-azacytidine and decitabine). Five hundred and seventeen patients were excluded since they received chemotherapy at a median of 17 months prior to AML diagnosis. In that group, only 35 of 517 patients had myelodysplastic syndrome (MDS) prior to AML diagnosis, and due to limitations of the data, it was not possible to determine the primary disorder that required chemotherapy. Excluding those 517 patients who had therapy preceding the month of AML diagnosis left 5,480 patients for inclusion in the outcome analysis.

End points

The primary end point was overall survival (OS) after AML diagnosis. Diagnosis date (month/year) was based on dates recorded in the SEER Patient Entitlement and Diagnosis Summary File. The date of death was assigned using the Medicare files (month/year) because follow-up information on mortality was available from Medicare for all patients through 2009. All other patients were censored at the end of observation (31st December 2009). We measured survival time from assigned date of diagnosis until death or last follow up. Secondary end points were: 1) receipt of leukemia therapy for AML within three months of diagnosis; 2) early death (ED) within two months of diagnosis; and 3) ED within two months after receiving leukemia therapy for AML.

Patients' characteristics

Patients' demographic, clinical and socio-economic characteris-

tics are described in Table 1. We categorized patients into 5-year age increments using age at diagnosis. We obtained data on race/ethnicity and metropolitan statistical area as recorded by SEER. Median annual household income and percentage of those aged 25 years or older with some college education at the ZIP code level from the 2000 US Census was used as a proxy for socio-economic status. We used the Medicare records to calculate an NCI Comorbidity Index score for each patient.[24,25] This approach[26,27] entails first removing claims that are considered to have unreliable diagnosis coding, such as those for testing procedures used to rule out conditions. Then, remaining diagnosis and procedure codes are used to identify the 15 non-cancer comorbidities in the Charlson comorbidity index (CCI).[28] The algorithms used to identify these conditions reflect the Deyo[29] adaptation of the CCI, and include several procedure codes from the Romano[30] adaptation. A weight is assigned to each condition, and the weights are summed to obtain the index for each patient.

History of MDS prior to AML diagnosis was identified only through Medicare records because SEER guidelines did not permit coding of multiple myeloid malignancies as multiple primaries until January 2010 (after this study period) leading to underrepresentation of MDS cases in the registry. The use of diagnostic procedures were also identified through Medicare files and a time period of ±2 months from the date of AML diagnosis was required for each test to associate with the AML diagnosis. This time restriction was not applied to human leukocyte antigen (HLA) testing which was used to estimate whether allo-HCT had been considered and whether a donor search had been initiated at any time point after AML diagnosis.

Table 1. Demographics and clinical characteristics of AML patients.

	Study cohort (n=5480) N (%)	Untreated group (n=3367) N (%)	Treated group (n=2113) N (%)	P
Age, years				
65-69	763 (13.9)	251(7.5)	512 (24.2)	
70-74	1139 (20.8)	512 (15.2)	627 (29.7)	
75-79	1293 (23.6)	768 (22.8)	525 (24.8)	
≥80	2285 (41.7)	1836 (54.85	449(21.3)	<0.01
Sex				
Male	2859 (52.2)	1676 (49.8)	1183 (56.0)	
Female	2621 (47.8)	1691 (50.2)	930 (44.0)	<0.01
Race/ethnicity				
White	4783 (87.3)	2928 (87.0)	1855 (87.8)	
Black	310 (5.7)	205 (6.1)	105 (5.0)	
Hispanic	95 (1.7)	56 (1.7)	39 (1.8)	
Other/unknown	292(5.3)	178 (5.3)	114 (5.4)	0.07
Metropolitan statistical area				
Large metro	3079 (56.2)	1898 (56.4)	1181 (55.9)	
Metro	1521 (27.8)	940 (27.9)	581 (27.5)	
Urban	330 (6.0)	213 (6.3)	117 (5.5)	
Less urban	446 (8.1)	264 (7.8)	182 (8.6)	
Rural	104 (1.9)	52 (1.5)	52 (2.5)	0.09
Median income*				
0-$35033.4	1367 (24.9)	867 (25.7)	500 (23.8)	
$ 35033.5-46202	1368 (24.9)	861 (25.6)	507 (24.1)	
$ 46203-52121	1367 (24.9)	841 (25.0)	526 (25.0)	
≥ $52122	1367 (24.9)	798 (23.7)	569 (27.1)	0.08
% Adults with some college education*				
0-22.5	1364 (24.9)	813 (24.1)	551 (26.1)	
22.6-27.9	1374(25.1)	860 (25.5)	514 (25.1)	
28.0-33.5	1373 (25.0)	838 (24.9)	535 (25.3)	
33.6-100	1369 (25.0)	856 (25.4)	513 (24.3)	0.1
Charlson comorbidity index (CCI) score				
0	3017 (55.0)	1720 (51.1)	1297 (61.4)	
1	1324 (24.2)	835 (24.8)	489 (23.1)	
≥2	1139 (20.8)	812 (24.1)	327 (15.5)	<0.01
Previous myelodysplastic syndrome				
No	4524 (82.5)	2698 (80.1)	1826 (86.4)	
Yes	959 (17.5)	669 (19.9)	287(13.6)	0.01
Use of hypomethylating agents by diagnosis year**				
2005	18 (2.7)	-	18 (7.3)	
2006	41 (6.2)	-	41 (15.9)	
2007	69(10.4)	-	69 (24.3)	

*Determined by average zip code level information according to 2000 United States census data.
** Use of hypomethylating agents within three months following AML diagnosis in 2005-2007.

Statistical analysis

Patients' characteristics were compared between the treated and untreated groups using the χ^2 test for categorical variables and t-test for continuous variables. A logistical regression model was used to evaluate the likelihood of: i) receipt of leukemia therapy for AML; ii) ED within two months after AML diagnosis; and iii) ED after receiving leukemia therapy. The covariates of interest included age, gender, race/ethnicity, CCI, education, median income, metropolitan statistical area size and history of MDS.

Unadjusted Kaplan-Meier survival plots were used for OS in the entire cohort and treatment groups as defined. Cox's proportional hazards regression model was used to evaluate the independent effects of covariates including leukemia therapy, age, gender, race/ethnicity, CCI, education, median income, metropolitan statistical area size and history of MDS on survival. Statistical analyses were performed using STATA system for Windows version 11.2.

Results

Description of study cohort

A total of 5,480 patients were identified as eligible for inclusion within the SEER-Medicare databases (Table 1). The study cohort included only older adults, with a median age at diagnosis of 78 years (interquartile range, IQR, 72-83). The frequency of prior MDS diagnosis increased with older age: 65-69 years (13.5%), 70-74 (17.2%), 75-79 (17.9%), and 80 years and over (18.6%) (P=0.01). Although half of all patients had a CCI score of 0, the score progressively worsened with age (Figure 1A).

Diagnostic testing

Diagnostic procedures included bone marrow aspiration and/or biopsy in 3,826 (69.8%), immunophenotyping in 3,222 (58.9%), and cytogenetics in 1,915 patients (34.9%). HLA typing was performed in only 130 (2.4%) patients. Diagnostic procedures, especially HLA typing, were more commonly performed on younger AML patients (*Online Supplementary Table S3*).

Leukemia therapy

Of all the 5,480 eligible patients, 2,113 (38.6%) received leukemia therapy for AML within three months of diagnosis and were designated as the 'treated group' (Table 1). Notably, patients aged 65-69 years with a CCI score of 0 received leukemia therapy over three times more often than patients aged 80 years and over with the same CCI score (Figure 1B). Multivariate analysis confirmed that a lower rate of leukemia therapy was associated with older age, higher CCI scores, previous MDS diagnosis, and

lower income level (Table 2).

In cases diagnosed in the years 2005-2007, a change in treatment approach was observed with 10.7% of all AML patients receiving either decitabine or 5-azacytidine after diagnosis. Of 211 patients, 128 (60.7%) received the therapy within three months after AML diagnosis (hypomethylating group). Compared with the rest of the treated group in 2005-2007, the hypomethylating group was older (median age 77 *vs.* 74; $P<0.01$) and more were white race (91.4% *vs.* 84.2%; $P=0.03$). Although there were more frequent prior diagnoses of MDS in the hypomethylating group, this difference did not reach statistical significance (13.3% *vs.* 8.5%; $P=0.09$). The other characteristics including education level, median income and CCI were similarly distributed between the hypomethylating and the chemotherapy-treated groups.

Early death after diagnosis and leukemia therapy

Early death (ED, within two months after diagnosis) was observed in 52.7% of older AML patients. In multivariate analysis, factors associated with ED after diagnosis in the untreated group included older age, female sex and worse CCI (Table 2). To compare ED after diagnosis in the treated group *versus* the untreated group, the treated group was limited to patients who received leukemia therapy in the same month of diagnosis to minimize time to leukemia therapy selection bias. With this rule applied, we observed a lower rate of ED after diagnosis in all subgroups of the treated group ($P<0.03$), except patients with CCI of 2 and over and age 80 years and over ($P=0.9$) (Figure 2A).

ED within two months after initiation of leukemia therapy was seen in 37.5% of patients and was associated with older age ($P<0.01$) and higher CCI scores ($P<0.01$). When adjusted for other variables, a similar observation with a higher relative risk of ED was noted in older patients with higher CCI scores (Table 2).

The ED rate was also analyzed separately for the hypomethylating group. After 2004, of 128 patients, ED was recorded for 24 (18.7%); this was lower than in the chemotherapy group (36%, $P<0.01$). The ED rate after hypomethylating agents was associated with increasing age: 65-69 years (11.8%), 70-74 (12.9%), 75-79 (15.8%), and 80 years and over (28%). This increase in ED was significant for patients aged 80 years and over compared with younger patients ($P=0.05$).

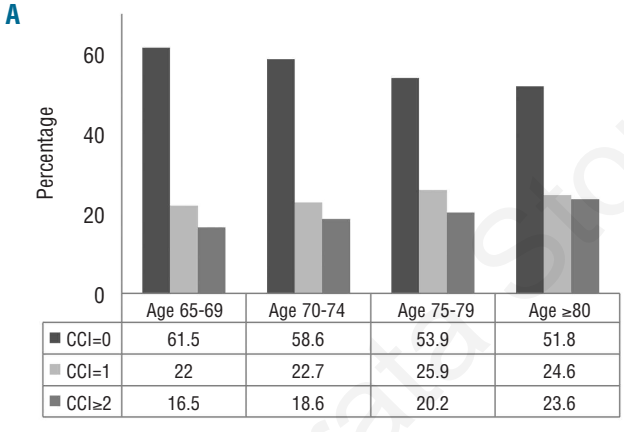


Figure 1. Frequency of Charlson comorbidity index (CCI) by age (A) and frequency of leukemia therapy use by age and CCI (B). Although half of all patients had a Charlson comorbidity index (CCI) score of 0, the score progressively worsened with age and there was a strong association of less leukemia therapy and older age with worse CCI.

Overall survival

The median OS following diagnosis was three months for the entire study cohort (IQR 1-10 months). Median OS was six months in the treated group compared with only two months in the untreated group ($P<0.01$) (Figure 3A). This improvement in OS after leukemia therapy was apparent in all age cohorts under the age of 80 years (Figure 3B), with a significant prolongation in median survival by six months in those aged 65-69 years (10 months *vs.* 4 months, $P<0.01$), five months in those aged 70-74 years (8 months *vs.* 3 months, $P<0.01$) and 4 months in those aged 75-79 years (6 months *vs.* 2 months, $P<0.01$). After 2004, among the patients receiving hypomethylating agents within the treated group, the median survival was nine months (IQR 2-17), which was similar to the 6-month median survival of patients treated with chemotherapy (IQR 2-15; $P=0.5$).

Cox's regression analysis, performed to identify prognostic factors for OS of the whole cohort, revealed that not only receiving leukemia therapy and younger age, but also lower CCI, higher median income and absence of previous MDS diagnosis were all associated with improved survival (Table 3, Figure 3C and D).

Allogeneic hematopoietic cell transplantation

Allo-HCT was performed in only 46 (0.8%) patients. Compared with the rest of the cohort, allo-HCT patients were younger (median age 67 *vs.* 78, $P<0.01$). They also had higher median income ($54810 *vs.* $46203; $P=0.01$) and more frequently CCI of 0-1 (100% *vs.* 79%; $P<0.01$). Their other characteristics were similar to the rest of the cohort. The median time from diagnosis to allo-HCT was 6.5 months (IQR 4-15), and the median time from first leukemia therapy to allo-HCT was five months (IQR 3-15). For the allo-HCT recipients, OS after diagnosis was 22 months (IQR 10-41). This improvement in OS after diagnosis was not associated with age ($P=0.6$), but it was associated with a lower CCI score ($P=0.05$). While allo-HCT recipients aged 65-69 and 70-74 years had similar median survival times of 29 and 22 months, transplanted patients with a CCI of 1 had markedly shorter survival (median 8 months) in contrast to those with a CCI score of 0 (median 29 months). Two-year survival after diagno-

Table 2. Logistical regression models for receiving leukemia therapy, early death after diagnosis* and early death after leukemia therapy.

Variable	Receiving leukemia therapy RR	95% CI	P	Early death after diagnosis* RR	95% CI	P	Early death after leukemia therapy RR	95% CI	P
Age group									
65-69	Reference			Reference			Reference		
70-74	0.6	0.5-0.7	<0.01	1.4	1.0-1.9	0.04	1.2	0.9-1.5	0.2
75-79	0.3	0.3-0.4	<0.01	1.5	1.4-2.0	<0.01	1.7	1.3-2.3	<0.01
≥80	0.1	0.1-0.14	<0.01	2.0	1.6-2.7	<0.01	3.1	2.4-4.1	<0.01
Sex									
Male	Reference			Reference			Reference		
Female	0.9	0.8-1.0	0.1	1.2	1.1-1.4	<0.01	0.8	0.7-1.0	0.08
Metropolitan statistical area									
Large metro	Reference			Reference			Reference		
Metro	1.0	0.8-1.1	0.7	1.1	0.9-1.3	0.2	1.0	0.8-1.2	0.9
Urban	0.9	0.7-1.2	0.4	0.9	0.7-1.3	0.6	0.9	0.6-1.4	0.6
Less urban	1.1	0.9-1.4	0.8	0.8	0.6-1.2	0.3	0.8	0.6-1.2	0.3
Rural	1.6	1.0-2.4	0.04	1.0	0.6-1.9	0.9	0.6	0.3-1.1	0.09
Race/ethnicity									
White	Reference			Reference			Reference		
Black	0.8	0.0-1.0	0.1	0.9	0.7-1.3	0.7	0.7	0.4-1.0	0.07
Hispanic	1.2	0.8-1.9	0.3	0.9	0.5-1.6	0.8	0.7	0.4-1.4	0.4
Other/unknown	0.9	0.7-1.2	0.5	0.6	0.5-0.9	<0.01	0.5	0.3-0.8	0.01
Median income**									
0-$35033.4	Reference			Reference			Reference		
$ 35033.5-46202	1.1	1.0-1.4	0.2	1.0	0.8-1.3	0.9	0.9	0.7-1.2	0.4
$ 46203-52121	1.2	0.9-1.4	0.2	0.9	0.7-1.2	0.5	1.1	0.7-1.5	0.8
≥ $52122	1.4	1.1-1.6	<0.01	0.9	0.7-1.1	0.2	0.8	0.6-1.1	0.1
% Adults with some college education**									
0-22.5	Reference			Reference			Reference		
22.6-27.9	0.9	0.8-1.1	0.2	0.8	0.7-1.0	0.06	0.9	0.7-1.2	0.5
28.0-33.5	0.9	0.8-1.1	0.2	0.9	0.7-1.1	0.5	0.9	0.7-1.2	0.4
33.6-100	0.8	0.7-0.97	0.03	1.0	0.8-1.2	0.9	0.9	0.7-1.2	0.4
Charlson comorbidity index (CCI) score									
0	Reference			Reference			Reference		
1	0.8	0.7-0.9	0.01	1.3	1.1-1.6	<0.01	1.3	1.1-1.7	0.01
≥2	0.6	0.5-0.7	<0.01	1.9	1.6-2.3	<0.01	1.8	1.4-2.4	<0.01
Previous myelodysplastic syndrome									
No	Reference			Reference			Reference		
Yes	0.7	0.5-0.8	<0.01	0.9	0.7-1.1	0.2	1.1	0.9-1.5	0.4

*For early death after diagnosis, the multivariate analysis was only performed in 'untreated' group. ** Determined by average zip code level information according to 2000 US census data. RR: Relative Risk; CI: confidence interval.

sis and after allo-HCT was 50% (95% CI: 35-63%) and 30.5% (95% CI: 17-45%), respectively.

Discussion

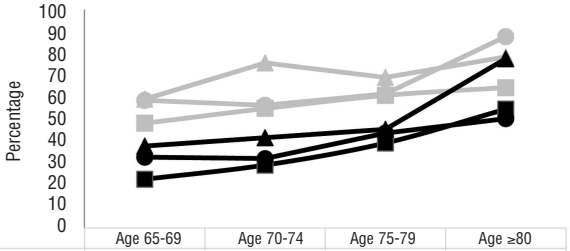
Although older age by itself is perhaps the most important adverse prognostic factor for AML,[6] it is insufficient to fully explain the poor outcomes observed in the older AML population. A higher frequency of poor performance status, secondary leukemia, preceding MDS, overexpression of P-glycoprotein, adverse cytogenetics, splenomegaly, and extramedullary disease can independently contribute to the observed poor outcomes.[31-33] In our study cohort, we were able to confirm that approximately 45% of older AML patients had comorbid illnesses and 17.5% had a previous diagnosis of MDS; both were associated with increasing age. On the other hand, the frequency of previous MDS diagnosis was relatively low considering that even in the absence of a clear previous hematologic disorder, trilineage myelodysplasia may be recognized morphologically in as many as 30% older patients with *de novo* AML.[34,35] These findings can be explained, at least in part by: i) the methodological limitations of using Medicare claim files to capture diagnosis of MDS;[36] and ii) exclusion of patients with first primary cancer diagnosis other than AML. We were not able to analyze other relevant prognostic factors due to limitations of the available population-based data.

Optimally, cytogenetics and other biological indicators would inform the initial management of untreated AML. For example, older patients with adverse cytogenetic features have complete remission rates of 32% and OS of 4%, indicating that they may be more suitable for investigational therapy.[33] More recent data suggest that there is no deterioration in outcome following a brief delay to determine the leukemic phenotype.[37] Although in our cohort only 34.9% of patients had cytogenetic testing, we hope that such data will improve its use in AML patients, along with immunophenotype and molecular classifica-

tion, and help design treatment plans on the basis of informative results.

We observed a modest increase in the use of leukemia therapy from the 33.8% reported by Lang *et al.*[9] to the 38.4% over the last decade reported in our study. Although the intention behind leukemia therapy could not be directly discerned, by limiting the time frame to three months after AML diagnosis, we likely improved the identification of patients treated with therapy intended to induce remission. However, we were not able to identify the subgroup of patients treated with subcutaneously administered, low-dose cytarabine which has been used as a lower intensity AML treatment for more than 25 years, and has been shown to improve overall survival compared to hydroxyurea and supportive care.[38,39]

Additionally, given that nearly 16.3% of the treated group diagnosed in 2005-2007 received hypomethylating agents, generally not classified as intensive induction therapy, induction therapy currently used in this older population is substantially fewer than the 38.4%.



	Age 65-69	Age 70-74	Age 75-79	Age ≥80
No therapy, CCI=0	47.9	54.7	60.7	64.3
No therapy, CCI=1	58.5	56.1	61.5	87.8
No therapy, CCI=2	58.9	75.6	69	78.3
Therapy, CCI=0	22.3	28.8	38.9	54.4
Therapy, CCI=1	32.4	31.8	43.4	50
Therapy, CCI=2	37.5	41.3	45.2	77.5

Figure 2. Early death rates after AML diagnosis by age and by Charlson comorbidity index (CCI). The treated group was restricted to patients who received leukemia therapy during the same month of AML diagnosis to minimize time to leukemia therapy selection bias.

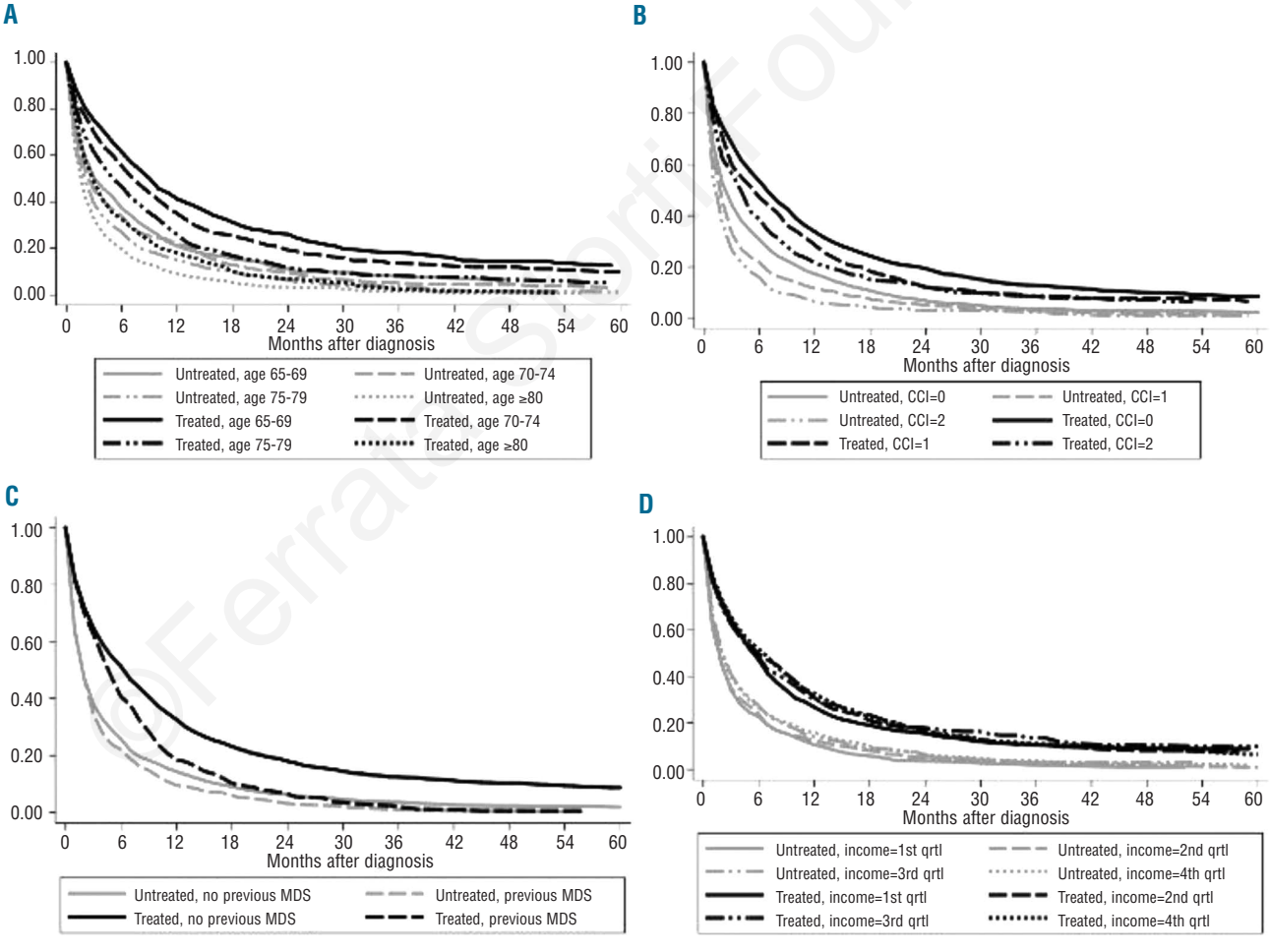


Figure 3. Overall survival by leukemia therapy stratified by age (A) Charlson comorbidity index (CCI) (B) previous MDS diagnosis (C) and median income (categorized by quartiles (qrtl)) (D). Median survival was six months longer in patients aged 65-69 (10 *vs.* 4 mo), five months in age 70-74 (8 mo *vs.* 3 mo), four months in 75-79 (6 mo *vs.* 2 mo) and two months in ≥80 (3 mo *vs.* 1 mo). (A) Patients with CCI of 0 to 1 had improved survival with chemotherapy (7 mo *vs.* 3 mo and 6 mo *vs.* 2 mo). However this improvement was less in patients with CCI ≥2 (4 mo *vs.* 2 mo). (B) Survival was better with therapy, even in patients with previous history of myelodysplastic syndrome (MDS) (5 mo *vs.* 2 mo); similar to patients with no previous MDS (7 mo *vs.* 2 mo). (C) With every quartile of some college education at the ZIP code level, improvement in survival observed with therapy (6 mo *vs.* 2 mo in first, second and fourth quartiles and 7 mo *vs.* 2 mo in the third quartile).

Table 3. Cox's regression model for overall survival.

Variable	RR	95% CI	P
Leukemia therapy			
No	Reference		
Yes	1.43	1.34-1.53	<0.01
Age group			
65-69	Reference		
70-74	0.81	0.75-0.87	<0.01
75-79	0.66	0.65-0.72	<0.01
≥80	0.57	0.53-0.63	<0.01
Charlson comorbidity index score			
0	Reference		
1	0.86	0.74-0.94	<0.01
≥2	0.75	0.69-0.81	<0.01
Median income*			
0-$35033.4	Reference		
$ 35033.5-46202	0.99	0.90-1.10	0.9
$ 46203-52121	1.06	0.98-1.14	0.1
≥ $52122	1.10	1.02-1.2	<0.01
Previous myelodysplastic syndrome			
No	Reference		
Yes	0.84	0.77-0.91	<0.01

*Determined by average zip code level information according to 2000 US census data. RR: relative risk; CI: confidence interval.

Many oncologists are reluctant to offer intensive chemotherapy to older patients considering that: i) most trials exclude AML patients aged over 55-60 years;[40] ii) high ED rates with 3- to 5-year survival rates of less than 10% have been reported;[34,40-42] and iii) increased comorbidities lead to higher morbidity and mortality. In our population-based study, we showed that receiving leukemia therapy was not only associated with younger age and lower CCI scores, but also with other demographic characteristics, such as male sex and higher median income level.

The risk of ED after AML therapy can also define a group of patients that can benefit from leukemia therapy. Kantarjian *et al.* have suggested that an analysis of death rates be conducted within eight weeks to include consideration of death rates resulting from lack of response.[31] In our comparison of ED within two months of diagnosis, we showed substantially reduced ED rates in those receiving leukemia therapy. This improvement was seen in all age groups under 80 years and with all CCI scores. Our results were similar to an analysis of the Swedish Acute Leukemia Registry[2] suggesting that denying therapy in older AML patients is inappropriate if based on presumed high rates of ED. Importantly, however, in patients older than 75 years or with higher CCI scores, the high ED rates after leukemia therapy (approx. 40% or higher) suggest caution in the use of such therapy, despite the observed improvement compared to the untreated group.

Survival for older AML patients varies depending on patients' and disease characteristics. Different groups have proposed prognostic modeling to estimate expected survival, in which age, cytogenetics, performance status and prior MDS are usually included. Recently, Kantarjian *et al.*[43] reported the MD Anderson experience in older AML patients (age ≥70 years) with 8-week mortality of 36% and OS of 4.6 months after leukemia treatment. In their analysis, only patients with favorable cytogenetics or those without poor risk features (age ≥80 years, complex cytogenetics, poor performance and creatinine level ≥ 1.3 mg/dL) had acceptable outcomes. Their conclusions were that, although intensive chemotherapy could be delivered to older patients with AML, it might not be beneficial for most, and it could be harmful to some. On the other hand, the Swedish Acute Leukemia Registry[2] reported long-term survivors among older AML patients given intensive treatment despite poor initial performance status (PS) of 3 or 4. Their results were encouraging, especially in older patients fit for chemotherapy with PS of 0-2, who had median OS of approximately 13 and 6 months in the 66-75 years and the 75 and over years age groups, respectively.

The SEER-Medicare data are true population-based data and provide a valid source for information currently available on older AML patients in the US. However, the data are limited and do not provide: i) detailed disease characteristics; ii) physician assessment at diagnosis about patients' fitness for chemotherapy; and iii) details of specific drug combinations used for induction. However, survival data are complete and allow CCI analysis to be performed, providing greater potential for informing treatment decisions than performance status alone. In addition, in contrast to most other reports, these data provide information on all AML patients irrespective of their management. Therefore, our analysis provides comprehensive data from a large and unselected older AML population in the US, both treated and untreated. These data are unique and widen our understanding of treatment decisions for the older AML population. With these data, we were able to confirm the developing view that leukemia therapy improves survival in older patients, even those aged up to 80 years, compared to other approaches.[34,41,42,44]

During recent years, several investigational agents have been explored for patients who are considered unfit for intensive chemotherapy.[11-13,39,45,46] In our cohort, we observed the rapid introduction of hypomethylating agents into practice, even in 2006 and 2007, before there was any mature published data on their use in AML. Although the definition of patients not fit for intensive chemotherapy may be subjective and vary according to the opinion of the individual physician, patients' preference or poor performance status with serious comorbidities, we can infer that our hypomethylating group actually represented those less fit, as they were older and had more prior MDS compared to the chemotherapy group. Among AML patients receiving hypomethylating agents in 2005-2007, the observed median OS was nine months, with only 18.7% ED. Despite their adverse prognostic factors, these results are encouraging and support the view that a subgroup of patients might enjoy longer survival using these agents and be spared some of the risks associated with traditional intensive induction therapy.

For selected older patients with AML, allo-HCT using reduced intensity conditioning (RIC) may represent an important and potentially curative approach. However, we observed that only 0.8% of patients in our cohort received an allo-HCT and noted that HLA testing, which can be used as a surrogate marker for consideration of allo-HCT, was performed in only 2.4% of all patients. Recently, Estey *et al.*[47] showed similar findings; only 14 of 259 AML patients (5.4%) over the age of 50 years underwent allo-HCT at the MD Anderson Cancer Center, a tertiary academic center. This is most likely due to concerns about the increased morbidity and mortality associated with allo-HCT in older patients. This presumption may

be partially countered by the recent findings of McClune *et al.* showing that transplantation toxicity, relapse, and survival for older adults are not significantly different from those for younger adults, even in patients aged over 65 years.[48] Despite the limitations in our data, the observed median survival with allo-HCT of 22 months was encouraging and exceeded the median survival achieved with any leukemia therapy.

In this large, population-based study of older AML patients, we found that many older AML patients are not fully evaluated at diagnosis, and most do not receive leukemia therapy. Although the results of therapy remain unsatisfactory, even in this older group their survival is markedly prolonged with leukemia therapy, and for a few with allo-HCT. The perception of older AML as an untreatable disease has to change. Individualized management based on comorbidity scores and phenotypically defined subgroups should be studied and widely implemented. Clinical therapies using novel agents should be the priority for patients less likely to benefit from intensive therapy, while for medically fit patients, modern intensive therapy followed by allo-HCT should be considered. We hope that the next decade will see an improvement in the approach to treatment for older AML patients based upon proper diagnostic prognostication and a broader application of currently available and new therapies.

Authorship and Disclosures

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