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Real World Treatment Patterns and Comparative Effectiveness among Elderly Patients with Acute Myeloid Leukemia in the United States

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Abstract

An evaluation of treatment patterns and outcomes among 11,142 first primary Acute Myeloid Leukemia (AML) patients was conducted. There were 936 (8%) patients who were treated with azacitidine and/or decitabine (HMA), 153 (1%) received a cytarabine combination regimen (Intensive), 433 (4%) received another type of agent (Other), 3250 (29%) received an unidentified agent (Unknown) and 6,370 (57%) did not receive any treatment. There were 403 (8%) patients who underwent subsequent allogeneic Hematopoietic Stem Cell Transplantation (HSCT) therapy after initial chemotherapy. Overall, treatment rates increased over the study time-period from 36% in 2000 to 55% in 2013 (P <0.0001). Treated patients were more likely to be younger, male, and married, and were less likely to have secondary AML, poor performance, and comorbid conditions compared to untreated patients. Receipt of all types of antileukemic therapy showed significant mortality risk reductions compared with palliative care. HSCT was associated with a 40% mortality risk reduction versus chemotherapy only, and the survival benefit was more pronounced among patients ≤75 years. These findings provide a rationale to strongly consider anti-leukemic therapy rather than best supportive care in older patients who do not meet criteria for more intensive regimens.

Keywords: Acute myeloid leukemia; chemotherapy; hematopoietic stem cell transplantation, treatment, survival, elderly patients

Introduction

The incidence of Acute Myeloid Leukemia (AML) increases with age and over half of patients are diagnosed at age ≥65 years [1]. Although AML is a relatively rare disease accounting for just over 1% of adult cancer deaths in the United States [2], the incidence is expected to increase as the population ages. The prognosis of patients 65 years and older is very poor and worsens with advancing age as treatment efficacy and tolerability have been shown to deteriorate markedly in older adults. Without treatment, AML progresses rapidly and is fatal within a few weeks of diagnosis [3]. There is no optimal treatment strategies for older patients with AML so therapy is individualized based on medical fitness, age, cytogenetic/molecular testing, the potential benefits for short and long-term outcomes, and the potential risk of adverse events in the context of patient wishes and socio-economic support.

Conventional intensive chemotherapy remains the standard of care for younger, functionally fit patients. Older patients, however, are often not treated or given less intensive chemotherapy and have inferior clinical outcomes. In spite of these facts, the major causes of death from AML in older patients are from infection and hemorrhage related to disease-associated cytopenias [4]. Retrospective and population-based studies suggest that age is not a barrier to the beneficial effects of AML treatment in patients up to 80 years old [5,6] and others have reported high rates of response and improved survival with intensive therapy up to 90 years old [7,8]. In addition, allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is often the only curative treatment modality for most AML patients older than 60 years [9-11]. Unfortunately, the majority of patients remain ineligible for HSCT.

Prospective studies may be subject to bias due to selection of younger and prognostically favorable patients receiving treatment. Randomized trials for AML patients 65 years and older are few, but have demonstrated a longer overall survival for intensively treated patients [12,13]. Prior population based analyses found that the use of chemotherapy has increased over time and was associated with a significant survival benefit compared to best supportive care [3,5]. However, there has been minimal improvement in survival as treatment strategies have not significantly changed for the past several decades ago. The goal of the study was to assess comparative effectiveness of existing therapeutic regimens, the patient characteristics associated with treatment receipt, and determine if treatment rates and survival continue to rise in a real-world population of elderly patients with AML.

Methods

Data sources

Data from the Surveillance, Epidemiology, and End Results (SEER) Medicare linked database was used for these analyses. Institutional Review Board (IRB) approval was waived because there are no personal identifiers in the SEER-Medicare database. The SEER-Medicare database is a collaborative effort of the National

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Cancer Institute (NCI), the SEER registries, and the Centers for Medicare & Medicaid Services and provides information on Medicare patients included in SEER, a nationally representative collection of 18 population-based registries of all incident cancers from diverse geographic areas [14]. The linked database includes all incident cancer patients reported to the SEER registries and cross-matched with a master file of enrollees in Medicare [15] with approximately 97% of persons 65 years or older eligible for Medicare. Inpatient care, skilled nursing care, home healthcare, and hospice care are covered services under Medicare Part A, while Part B reimburses for physician and outpatient care with about 95% of beneficiaries subscribing to Part B. The SEER-Medicare linkage used in this study include all Medicare eligible cancer patients reported to SEER through 2013 and their Medicare claims through 2015.

Study population

Patients were included if they were diagnosed with a first primary AML cancer from January 1, 2000 to December 31, 2013, >66 years, and continuously enrolled in Medicare Parts A and B with no HMO coverage in the year prior to diagnosis (Supplementary Figure 1). Patients were excluded if their date of death was recorded prior to or the same month as diagnosis, if they were enrolled in a Health Maintenance Organization (HMO) at any time during the 12 months prior to diagnosis (because complete claims data were unavailable for these patients), and if they had two or more claims for chemotherapy prior to diagnosis.

Study variables

The SEER program registries routinely collect data on patient demographics (age, race/ethnicity, residence, and socioeconomic status [income and education per census tract]); primary tumor site, tumor morphology and stage at diagnosis; first course of treatment, and follow-up for vital status. AML diagnosis was based on the International Classification of Disease for Oncology (3rd edition, ICD-O-3) histology codes in the SEER data. Median annual household income at the census tract level, and percentage of adults aged 25 or older with at least some college education at the ZIP code level in the SEER data were used as a proxy for socioeconomic status.

Risk stratification in AML is based on cytogenetics and molecular abnormalities, which were not available in the SEER data. Prior Myelodysplastic Syndrome (MDS) or Myeloproliferative Neoplasm (MPN) that transforms into AML are also poor prognostic features, and occur more commonly among elderly patients. [16] In the absence of disease stage, prior MDS was used as a proxy for high risk patients and was identified using diagnosis codes in Medicare Parts A and B claims files prior to AML diagnosis. By design, patients with therapy-related AML (t-AML) were excluded based on the inclusion criteria of the study cohort. SEER also does not include measures of performance status, such as Eastern Cooperative Oncology Group. Instead, we used Medicare claims to identify several indictors of Poor Performance status (PPI) [17], including the use of oxygen and related respiratory therapy supplies, wheelchair and supplies, home health agency services, and skilled nursing facility services that occurred 12 months prior to AML cancer diagnosis.

To assess baseline comorbidity burden, we utilized the National Cancer Institute (NCI) comorbidity index [18] to identify the 15 non-cancer comorbidities from the Charlson Comorbidity Index [19]. The index accounts for the number and seriousness of the conditions and a higher score indicates a greater burden of comorbid disease. Diagnosis and procedure codes were identified from Medicare claims one year prior to diagnosis and must appear on at least two different claims that are more than 30 days apart to ensure that "rule out" diagnoses are not counted as comorbid conditions.

Chemotherapy administration was identified using International Classification of Disease (9th revision), Clinical Modification (ICD-9-CM) diagnosis codes and procedural codes, and Healthcare Common Procedural Coding System (HCPCS) "J" codes were used to identify the specific drug administered [20]. The absence of these claims indicated lack of treatment. The first chemotherapy claim within three months from diagnosis indicated the start of therapy. Patients were classified into treatment groups based on all chemotherapy administered during the first 60 days after treatment initiation. Chemotherapy agent definition was not possible in approximately 70% of patients who received therapy because chemotherapy was administered during inpatient admissions, which are paid based on ICD-9 diagnosis or procedures codes only and not chemotherapy codes. Medicare claims files were also searched for ICD-9-CM and HCPCS codes to identify patients undergoing allogeneic Hematopoietic Stem Cell Transplantation (HSCT) anytime during follow-up.

Overall survival was measured from diagnosis date to date of death. The date of death was assigned by using the Medicare date or SEER date of death if Medicare date was missing. All other patients were assumed to be alive at the end of the follow-up period (December 31, 2015).

Statistical analysis

All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc., Cary, North Carolina). Demographic and clinical characteristics were summarized descriptively by treatment status (treated vs. not treated) and treatment type. Chi-square test for categorical variables and ANOVA or t-test for continuous variables determined differences between groups. We considered a p-value $<.05$ to be statistically significant.

In the overall survival analyses we made comparisons between the treated and not treated patients; between treated patients receiving HSCT and those who did not; and between those receiving low dose therapy with azacitidine or decitabine (HMA Therapy), aggressive induction therapy with a cytarabine combination regimen (Intensive Therapy), other type of agents including hydroxyurea, cytarabine only, gemtuzumab, arsenic trioxide, lenalidomide, clofarabine, rituximab, or vincristine (Other Therapy), an unidentified agent (Unknown Therapy) and those not receiving treatment (Not Treated). Kaplan-Meier survival curves and corresponding log-rank tests examined unadjusted overall survival by treatment group. Since timing of treatment initiation differed between patients, the relationship between treatment and survival was evaluated using a Cox regression model with treatment as a time-dependent factor. In the time-varying Cox model, all patients belong to the "not treated" group and only switched to the "treated" group at the time of treatment receipt. Other confounders included in the Cox model were selected a *priori* from baseline demographic and clinical characteristics.

Table 1: Baseline patient characteristics by treatment status and treatment type.

	Total (N = 11142)		Treated (N = 4772)	Not Treated (N = 6370)		HMA N = 936	Intensive N =153	Other N = 433	Unknown N = 3250	
	n	%	%	%	*p* [a]	%	%	%	%	*p* [b]
Age at Diagnosis										
66-70	2008	28.8	10.0	18.0	< 0.0001	15.7	41.8	20.8	33.0	< 0.0001
71-75	2390	28.5	16.2	21.5		23.0	29.4	23.3	30.7	
76-80	2586	23.2	23.2	23.2		27.2	16.3	24.2	22.2	
81-85	2243	13.2	25.3	20.1		24.1	12.4[c]	17.3	9.8	
>86	1915	6.3	25.3	17.2		9.9		14.3	4.3	
Sex										
Male	5810	54.4	50.4	52.1	< 0.0001	58.0	60.8	48.5	53.9	<0.0001
Female	5332	45.6	49.6	47.9		42.0	39.2	51.5	46.1	
Race/ethnicity										
White	9673	86.9	86.7	86.8	0.0301	88.6	88.2	85.9	86.6	0.0795
Black	681	5.5	6.5	6.1		4.4	11.7[c]	4.6	6.0	
Other/Unknown	788	7.5	6.7	7.1		7.1		9.5	7.4	
Prior MDS[1]										
No	9243	85.8	80.8	83.0	<0.0001	84.3	92.8	82.9	86.3	<0.0001
Yes	1899	14.2	19.2	17.0		15.7	7.2	17.1	13.7	
PPI[2]										
No	9573	92.4	81.1	85.9	<0.0001	89.5	100.0[c]	89.6	93.4	<0.0001
Yes	1569	7.6	18.9	14.1		10.5		10.4	6.6	
NCI Co-morbidity Score										
0	5303	53.5	43.2	47.6	<0.0001	44.8	54.9	50.8	56.3	<0.0001
1	2854	25.9	25.4	25.6		26.7	28.8	26.3	25.4	
2	1473	10.9	14.9	13.2		13.4	16.4[c]	12.7	10.0	
≥3	1512	9.7	16.5	13.6		15.2		10.2	8.3	
Marital Status										
Married	5796	60.4	45.7	52.0	<0.0001	59.4	71.9	54.7	60.9	<0.0001
Single	774	7.2	6.8	6.9		7.5	9.8[c]	5.5	7.4	
Separated/ Divorced	750	6.6	6.8	6.7		5.9		6.2	7.1	
Widowed	3273	21.3	35.4	29.4		22.8	18.3[c]	28.4	20.3	
Unknown	549	4.4	5.3	4.9		4.5		5.1	4.4	
%of adults with some college education										
0-50	3354	29.7	30.4	30.1	0.6026	26.8	28.1	31.6	30.3	0.2363
51-100	7582	68.4	67.8	68.0		70.6	71.9[c]	68.3[c]	67.9	
Unknown	206	1.9	1.8	1.8		2.6			1.8	
Median Income Quartiles										
1-Low	2734	23.7	25.2	24.5	0.0051	20.4	24.2	28.9	23.9	0.0085
2	2734	24.5	24.6	24.5		25.1	23.5	23.8	24.4	
3	2735	23.8	25.1	24.5		24.5	28.1	21.0	23.8	
4-High	2733	26.1	23.3	24.5		27.5	24.2[c]	26.3[c]	26.0	
Unknown	206	1.9	1.8	1.8		2.6			1.8	
Geographic region										

Midwest	1124	11.0	9.4	10.1	0.0457	9.0	11.1	6.7	12.1	<0.0001
Northeast	680	6.3	5.9	6.1		6.2	9.2	6.7	6.2	
South	4131	36.6	37.4	37.1		34.4	29.4	34.9	37.8	
West	5207	46.1	47.2	46.7		50.4	50.3	51.7	43.9	

Abbreviations: NCI: National Cancer Institute; MDS: Prior Myelodysplastic Syndrome; PPI: Poor Performance Indicators.

[a]*p-value* Treated vs. Not Treated

[b]*p-value* Not Treated vs. HMA vs. Intensive vs. Other vs. Unknown

[c]Cells with counts of less than 11 are combined in compliance with the National Cancer Institute data use agreement for small cell sizes.

[1]Patients with a prior Myelodysplastic Syndrome (MDS) or myeloproliferative disease was identified from Medicare claims and was used as a proxy for high risk patients in the absence of disease stage.

[2]Poor Performance Indicators (PPI) were identified from Medicare claims and include the use of oxygen and related respiratory therapy supplies, wheelchair and supplies, home health agency services, and skilled nursing facility services that occurred 12 months prior to AML diagnosis.

To assess the risk of early death (30-day mortality and 60-day mortality) a Cox regression model with treatment as a time-dependent factor was constructed. The "treated" group was limited to patients who received treatment within 30 days after diagnosis to minimize the introduction of immortal time bias in the analysis (period of follow-up time during which death cannot occur) [21].

As a sensitivity exercise for the comparison between HMA Therapy, Intensive Therapy, Other Therapy, Unknown Therapy and No Treatment, we also conducted a propensity score-matched survival analysis. Multinomial logistic regression was used to calculate a propensity score the conditional probability that each patient would be assigned to a specific treatment group given that patient's pretreatment variables [22,23]. Pairwise matching was conducted where each patient receiving a specific therapy (HMA, Intensive, Other, or Unknown) was matched to one untreated patient. Matching variables were age, sex, race, marital status, education, geographic region, year diagnosed, prior MDS, poor performance indicators, and comorbidity score. Matched survival analysis was completed using the Cox proportional hazards regression model, stratifying on the matched pair.

In the survival models, follow-up was calculated beginning on the date of diagnosis up until the first occurrence of a censoring event: date of death, the last date for which Medicare claims are available, or the end of the follow-up period (December 31, 2015).

Results

Treatment trends over time

Of the 11,142 patients included in the study, 4,772 (43%) patients received anti-leukemic treatment with chemotherapy within 3 months of diagnosis and 6,370 (57%) patients did not receive any antileukemic treatment. Treatment rates increased over the study time period from 36% in 2000 to 55% in 2013 (p <0.0001). Of those initiating treatment, 936 (8%) could be confirmed to have been treated with azacitidine and/or decitabine (HMA), 153 (1%) were confirmed to receive treatment with a cytarabine combination regimen (Intensive), 433 (4%) received another type of agent (Other) and 3,250 (29%) received an unidentified agent (Unknown). From 2005 to 2013, use of HMA therapy significantly increased from 2% to 22%, while during the same time period, the proportion of patients who did not receive treatment significantly decreased from 63% to 45% (Figure 1). Rates of Intensive therapy remained fairly consistent throughout the entire study period. Of 4,772 patients initiating treatment, 403 (8%) eventually underwent HSCT therapy after chemotherapy and 4,369 (92%) did not. Rates of HSCT also increased over the study time period from 7% in 2000 to 12% in 2012 (p=0.0033).

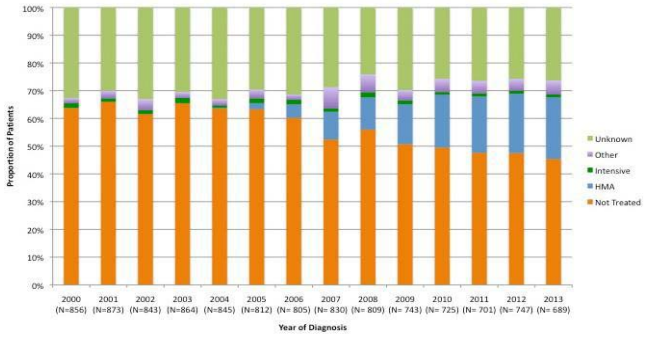

Figure 1: Therapy cohort by year of diagnosis.

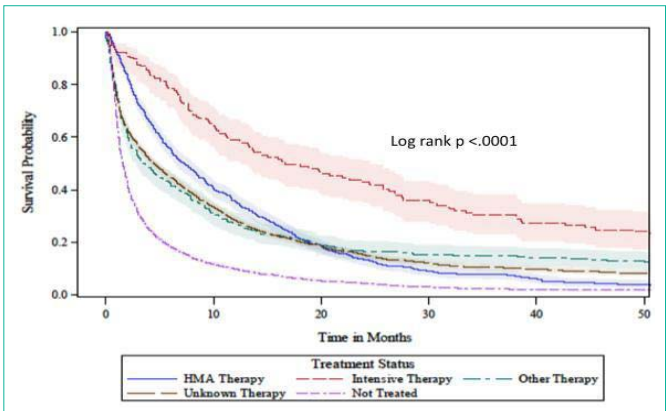

Figure 2: Unadjusted overall survival by treatment type.

Outcomes according to treatment status

The distribution of patient characteristics by treatment status is shown on (Table 1). The mean age at diagnosis was 75 years for treated patients and 80 years for untreated patients (P <0.0001). Forty-three percent of treated patients were over the age of 75 years at diagnosis compared with 74% of untreated patients. Treated patients were more likely to be male (54% vs. 50%), be married (60% vs. 46%), to have a lower incidence of prior MDS (14% vs. 19%), were less likely to have PPIs (8% vs. 19%), and had a lower comorbidity burden (54% vs. 43% with a comorbidity score of 0) compared with untreated patients.

The median unadjusted overall survival was 2.13 months (95% CI: 0.93-7.07) for the overall population and was longer for treated

Table 2: Baseline patient characteristics by HSCT status.

	All Treated			≤75 year olds			>75 year olds		
	HSCT N = 403	No HSCT N = 4369	*p*[a]	HSCT N = 329	No HSCT N = 2404	*p*[b]	HSCT N = 74	No HSCT N = 1965	*p*[c]
Age at Diagnosis	%	%		%	%		%	%	
66-70	55.1	26.4	<0.0001	67.5	47.9	<0.0001			0.8045
71-75	26.6	28.7		32.5	52.1				
76-80	10.4	24.4					56.8	54.2	
81-85	7.9[d]	13.9					43.3[d]	30.9	
>86		6.7						14.9	
Sex									
Male	62.5	53.7	0.0007	61.7	54.6	0.0153	66.2	52.6	0.0209
Female	37.5	46.3		38.3	45.4		33.8	47.4	
Race/ethnicity									
White	88.3	86.8	0.3577	88.4	85.8	0.1332	100.0[d]	88.0	0.9910
Black	4.0	5.7		4.0	6.9			4.2	
Other/Unknown	7.7	7.5		7.6	7.3			7.7	
Prior MDS[1]									
No	89.1	85.5	0.0507	89.4	86.8	0.1890	100.0[d]	84.0	0.3773
Yes	10.9	14.5		10.6	13.2			16.0	
PPI[2]									
No	96.0	92.0	0.0038	100.0[d]	94.0	0.0160	100.0[d]	89.6	0.7982
Yes	4.0	8.0			6.0			10.4	
NCI Co-morbidity Score									
0	59.3	53.0	0.0571	63.2	55.1	0.0217	41.9	50.4	0.3105
1	23.3	26.1		22.8	26.3		25.7	25.8	
2	7.9	11.2		6.4	10.4		14.9	12.2	
≥3	9.4	9.7		7.6	8.2		17.6	11.6	
Marital Status									
Single	7.4	7.2	0.0033	7.3	8.5	0.4024	59.5[d]	5.5	0.7146
Married	65.8	59.9		69.0	65.0			53.6	
Separated/Divorced	8.7	6.5		9.1	8.0		40.5[d]	4.5	
Widowed	14.1	22.0		10.9	13.9			31.9	
Unknown	4.0	4.5		3.6	4.5			4.5	
%of adults with some college education									
0-50	24.8	30.1	0.0748	24.3	32.2	0.0130	27.0	27.5	0.9402
51-100	75.1[d]	68.0		75.7[d]	65.8		73.0[d]	70.6	
Unknown		1.9			2.0			1.9	
Median Income Quartiles									
1-Low	19.9	24.0	0.0386	20.1	25.8	0.0004	18.9	21.9	0.4627
2	21.6	24.7		19.5	25.7		31.1	23.5	
3	27.0	23.5		27.7	23.5		24.3	23.6	
4-High	29.8	25.8		31.0	23.0		24.3	29.1	
Geographic region									
Midwest	10.2	11.0	0.0027	12.7[d]	10.8	0.0005	13.5[d]	11.3	0.8496
Northeast	2.7	6.6			7.7			5.4	
South	34.2	36.8		33.4	36.3		37.8	37.5	
West	52.9	45.5		53.8	45.3		48.6	45.8	

Abbreviations: AD: Azacitidine+Decitabine; CA: Cytarabine+Anthracycline; HSCT: Allogeneic Hematopoietic Stem Cell Transplantation; NCI: National Cancer Institute; MDS: Prior Myelodysplastic Syndrome; PPI: Poor Performance Indicators.
[a]*p-value* HSCT vs. No HSCT among all chemotherapy treated patients
[b]*p-value* HSCT vs. No HSCT among patients ≤75 year olds
[c]*p-value* HSCT vs. No HSCT among patients >75 year olds
[d]Cells with counts of less than 11 are combined in compliance with the National Cancer Institute data use agreement for small cell sizes
[1]Patients with a prior Myelodysplastic Syndrome (MDS) or myeloproliferative disease was identified from Medicare claims and was used as a proxy for high risk patients in the absence of disease stage.
[2]Poor Performance Indicators (PPI) were identified from Medicare claims and include the use of oxygen and related respiratory therapy supplies, wheelchair and supplies, home health agency services, and skilled nursing facility services that occurred 12 months prior to AML diagnosis

Table 3: Adjusted overall survival and risk of early death by treatment status.

Covariates	Overall Survival[a] N = 11,142			30-day mortality[ab] N = 11,142		60-day mortality[ab] N = 11,142	
	N	HR	95% CI	HR	95% CI	HR	95% CI
Treatment Status							
Not-treated (ref)	6370						
Treated	4772	0.860	0.81-0.91	0.333	0.29-0.38	0.593	0.55-0.64
Age at Diagnosis							
66-70 (ref)	2008						
71-75	2390	1.253	1.16-1.35	1.143	0.98-1.34	1.283	1.15-1.43
76-80	2586	1.502	1.39-1.62	1.178	1.01-1.37	1.404	1.26-1.56
81-85	2243	1.714	1.58-1.86	1.415	1.22-1.65	1.612	1.45-1.79
>86	1915	2.097	1.92-2.30	1.772	1.52-2.06	2.129	1.91-2.37
Sex							
Female (ref)	5332						
Male	5810	1.019	0.97-1.07	0.975	0.89-1.07	0.993	0.93-1.06
Race/ethnicity							
White (ref)	9673						
Black	681	0.840	0.75-0.94	0.777	0.64-0.94	0.874	0.77-0.99
Other/Unknown	788	0.850	0.77-0.94	0.874	0.74-1.04	0.834	0.74-0.94
Marital Status							
Married (ref)	5796						
Single	774	1.237	1.12-1.36	1.235	1.05-1.45	1.290	1.15-1.45
Separated/Divorced	750	1.201	1.09-1.32	1.310	1.11-1.54	1.218	1.08-1.37
Widowed	3273	1.176	1.11-1.25	1.135	1.02-1.26	1.158	1.08-1.25
Unknown	549	0.997	0.89-1.12	1.108	0.92-1.34	1.063	0.93-1.22
Prior MDS[1]							
No (ref)	9243						
Yes	1899	0.998	0.94-1.07	1.010	0.91-1.12	0.972	0.90-1.05
PPI[2]							
No (ref)	9573						
Yes	1569	1.205	1.12-1.30	1.398	1.26-1.56	1.306	1.21-1.41
NCI Co-morbidity Score							
0 (ref)	5303						
1	2854	1.150	1.08-1.22	1.069	0.96-1.19	1.106	1.03-1.19
2	1473	1.227	1.14-1.33	1.233	1.09-1.39	1.341	1.23-1.46
≥3	1512	1.324	1.22-1.44	1.352	1.20-1.53	1.400	1.28-1.53

Abbreviations: NCI: National Cancer Institute; MDS: Prior Myelodysplastic Syndrome; PPI: Poor Performance Indicators.
[1]Patients with a prior Myelodysplastic Syndrome (MDS) or myeloproliferative disease was identified from Medicare claims and was used as a proxy for high risk patients in the absence of disease stage.
[2]Poor Performance Indicators (PPI) were identified from Medicare claims and include the use of oxygen and related respiratory therapy supplies, wheelchair and

supplies, home health agency services, and skilled nursing facility services that occurred 12 months prior to AML diagnosis.
[a]Model also includes geographic region, income and year of diagnosis.
[b]Treated group restricted to patients who received treatment within 30 days after diagnosis.

patients (5.3 months, 95% CI: 5.0-5.8) compared with untreated patients (1.6 months, 95% CI 1.6-1.7; log-rank *P* <0.0001). In multivariate survival analysis (Table 3), treated patients exhibited a 14% lower risk of death compared with untreated patients (HR 0.86; 95% CI 0.81–0.91). Advanced age at diagnosis, higher comorbidity score, presence of PPIs, and being unmarried were significantly associated with higher mortality risk.

The multivariate analysis of factors predicting early death is shown in (Table 3). There were 2359 (21%) of patients who died within 30 days of diagnosis and 4743 (43%) that died within 60 days of diagnosis. Stratifying by treatment status, 263 (2%) treated patients and 2096 (19%) untreated patients died within 30 days of diagnosis. Treated patients had a 67% lower likelihood of early death within 30 days of diagnosis and a 41% lower likelihood of early death within 60 days of diagnosis compared to the untreated cohort. Other factors associated with increased risk of early death include older age, unmarried, higher comorbidity burden and presence of poor performance indicators.

Outcomes according to treatment modality

There were similarities in demographic and clinical characteristics between patients receiving Intensive and Unknown therapies and between patients receiving HMA, Other therapies, and those who were untreated (Table 1). Patients receiving Intensive chemotherapy and Unknown therapy were younger, had lower comorbidity burden, and were less likely to have prior Myelodysplastic Syndromes (MDS) or PPIs.

Figure 2 shows the median unadjusted overall survival was longest for patients receiving Intensive therapy (16.7 months), followed by HMA therapy (7.3 months), Unknown therapy (4.5 months), Other therapy (3.5 months), and was shortest for untreated patients (1.6 months; log-rank *p* <0.0001). After adjusting for age, sex, race, MDS, PPIs, comorbidity score, marital status, income, education, geographic region, and year of diagnosis in the survival model, receipt of all types of antileukemic therapy demonstrated significantly improved survival compared with palliative care or no treatment (Table 4). Compared to the untreated group, patients who received Intensive therapy had the largest statistically significant reduction in overall mortality risk (68%), followed by a 53% mortality risk reduction among patients who received HMA therapy, 51% among patients who received Other Therapy and 34% among those received an Unknown therapy type. The propensity score-matched survival model confirmed the significant improvement in overall survival among all treatment groups compared to no treatment. Intensive and HMA therapy groups have overlapping confidence intervals, but both groups exhibited statistically significant lower mortality risks compared to Other therapy and Unknown therapy groups.

Effect of allogeneic stem cell transplantation on survival

Of the 403 patients who underwent HSCT, the majority (82%) were aged ≤75 years (Table 2). Patients who underwent HSCT were younger at diagnosis, more likely to be male, more likely to be married, less likely to have prior MDS or PPIs, and had a lower comorbidity score versus patients treated with chemotherapy only. In a subset analysis stratified by age, the relationships observed between patient characteristics and HSCT receipt persisted in the younger cohort of patients (≤75 years) but not in the older cohort (>75 years).

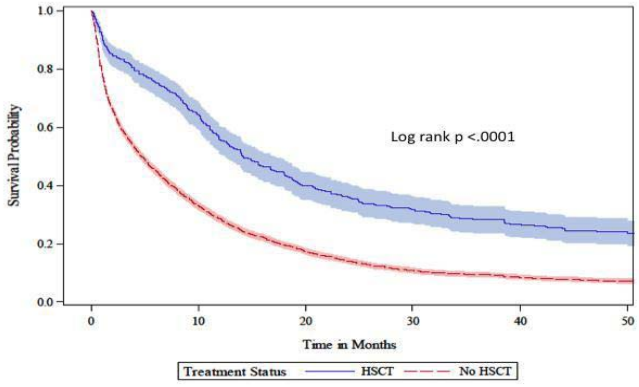

Figure 3a: Kaplan-Meier Curve of Overall Survival by HSCT.

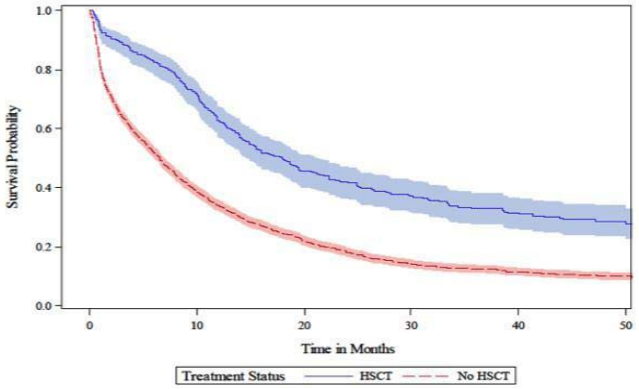

Figure 3b: Patients aged ≤75 years.

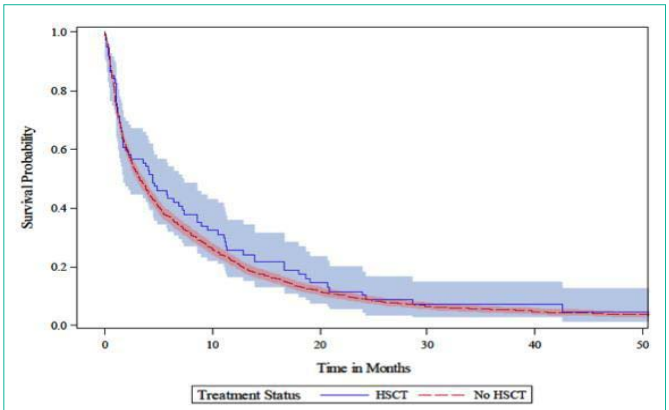

Figure 3c: Patients aged >75 years.

Figures 3a-c shows the unadjusted median overall survival was higher for the HSCT group (14.2 months) versus the non-HSCT group (4.8 months; log-rank *P* <0.0001). This relationship was corroborated in the younger aged cohort ≤75 years where the unadjusted median

Table 4: Adjusted overall survival by treatment type.

Covariates	N	Multivariate Cox Regressiona		Propensity-Weighted Cox Regressionb	
Subpopulation		HR	95% CI	HR	95% CI
Not Treated (ref)	6370				
HMA Therapy	936	0.471	0.43-0.52	0.529	0.49-0.57
Intensive Therapy	153	0.317	0.25-0.40	0.437	0.37-0.51
Other Therapy	433	0.490	0.43-0.56	0.692	0.63-0.77
Unknown Therapy	3250	0.660	0.62-0.70	0.742	0.71-0.77
Age at Diagnosis					
66-70 (ref)	2008				
71-75	2390	1.228	1.14-1.33		
76-80	2586	1.418	1.31-1.53		
81-85	2243	1.546	1.42-1.68		
>86	1915	1.793	1.64-1.97		
Sex					
Female (ref)	5332				
Male	5810	1.018	0.97-1.07		
Race/ethnicity					
White (ref)	9673				
Black	681	0.814	0.73-0.91		
Other/Unknown	788	0.837	0.76-0.92		
Marital Status					
Married (ref)	5796				
Single	774	1.226	1.11-1.35		
Separated/Divorced	750	1.144	1.04-1.26		
Widowed	3273	1.150	1.08-1.22		
Unknown	549	0.963	0.86-1.08		
Prior MDS[1]					
No (ref)	9243				
Yes	1899	0.977	0.92-1.04		
PPI[2]					
No (ref)	9573				
Yes	1569	1.146	1.06-1.24		
NCI Co-morbidity Score					
0 (ref)	5303				
1	2854	1.158	1.09-1.23		
2	1473	1.228	1.14-1.33		
≥3	1512	1.310	1.21-1.42		

Abbreviations: NCI: National Cancer Institute; MDS: Prior Myelodysplastic Syndrome; PPI: Poor Performance Indicators.

[1]Patients with a prior Myelodysplastic Syndrome (MDS) or myeloproliferative disease was identified from Medicare claims and was used as a proxy for high risk patients in the absence of disease stage.

[2]Poor Performance Indicators (PPI) were identified from Medicare claims and include the use of oxygen and related respiratory therapy supplies, wheelchair and supplies, home health agency services, and skilled nursing facility services that occurred 12 months prior to AML diagnosis.

[a]Model also includes geographic region, income and year of diagnosis.

[b]Propensity score weighted for age, sex, race, prior MDS, PPI, NCI comorbidity score, geographic region, income and year of diagnosis.

overall survival was higher for the HSCT group (17.9 months) versus the non-HSCT group (6.6 months; log-rank P <0.0001), but not in the older cohort aged >75 where the median overall survival was 4.5 months for the HSCT group vs. 3.3 months in the non-HSCT group (log rank p=0.3774).

In multivariate survival analysis (Table 5), patients who underwent HSCT had a 40% lower risk of death versus those who did not undergo HSCT (HR 0.60; 95% CI 0.53–0.67). Advanced age, male sex, higher comorbidity score, prior MDS, and PPIs were significantly associated with higher risk of mortality. Stratifying by age, the survival benefit with HSCT was only demonstrated in the younger cohort aged ≤75 years (HR 0.53; 95% CI 0.46–0.60) and no difference in mortality risk was noted in the older cohort aged >75 years (HR 0.85; 95% CI 0.67–1.08).

Discussion

We confirmed the observations from our original work [3] that the use anti-leukemic chemotherapy among elderly AML patients in real-world practice continues to increase. Most of this increase was driven by increased use of HMAs between 2005 and 2013 (from 2% to 22%), with a proportional reduction of untreated patients. Despite similar baseline characteristics in patients in the HMA, Other Therapy and Not Treated groups, treatment with HMAs and Other therapies were associated with statistically significant improvement in survival. Findings from a prior comparative observational study and a randomized trial support findings that azacitidine was associated with better survival compared to conventional care with intensive chemotherapy and BSC among poor-risk patients ages 65 years and older with newly diagnosed AML [24,25]. Even with increasing therapy use at the time of this analysis, nearly half (45%) of subjects still did not receive treatment, and the rate of no treatment was even more pronounced (74%) among patients >75 years at diagnosis. These observations highlight the need for novel therapies for AML patients with advancing age and co-morbidities, such as the recent FDA approval of BCL-2 inhibitors in combination with HMAs or low-dose intensive therapy for treatment of newly diagnosed AML patients who are ≥75 years of age, or had comorbidities that precluded the use of intensive induction chemotherapy due to comorbidities [26].

The current study went further to evaluate age-specific treatment patterns and outcomes surrounding use of HSCT. In the current study, 8% of AML patients that received antileukemic therapy subsequently underwent subsequent HSCT therapy with the majority (82%) being between 66-75 years of age. Rates of HSCT increased by 5% over the 12-year study time period. This is consistent with previous reports of a steady increase in HSCT utilization among patients 70 years and older [27]. In addition, others have also shown that advancing age may be associated with worse post-HSCT outcomes in patients with AML [28]. In the multivariate survival analysis, HSCT was associated with a 40% reduction in mortality risk versus patients receiving chemotherapy only; however, this survival benefit was limited to patients aged 66-75 years. In spite of these findings, our observations show an important survival benefit with HSCT in select older patients with AML.

Strengths & Limitations

Real-world observational studies are considered inferior to RCT's,

Table 5: Adjusted overall survival among treated patients with and without HSCT.

	Treated[a] N = 4772			≤75 years[a] N = 2733		>75 years[a] N = 2039	
HSCT	N	HR	95% CI	HR	95% CI	HR	95% CI
No (ref)	4369						
Yes	403	0.598	0.53-0.67	0.526	0.46-0.60	0.852	0.67-1.08
Age at Diagnosis							
66-70 (ref)	1374						
71-75	1359	1.204	1.11-1.30				
76-80	1108	1.450	1.33-1.58				
81-85	630	1.704	1.54-1.89				
>86	301	2.131	1.86-2.44				
Sex							
Female (ref)	2174						
Male	2598	1.111	1.04-1.18	1.110	1.02-1.21	1.104	1.00-1.22
Race/ethnicity							
White (ref)	4149						
Black	264	0.891	0.78-1.02	0.936	0.79-1.11	0.797	0.63-1.02
Other/Unknown	359	0.919	0.82-1.03	0.926	0.79-1.08	0.902	0.76-1.07
Marital Status							
Married (ref)	2882						
Single	343	1.184	1.05-1.33	1.148	0.99-1.34	1.120	0.92-1.37
Separated/Divorced	317	1.285	1.14-1.45	1.176	1.01-1.36	1.473	1.19-1.83
Widowed	1018	1.197	1.10-1.30	1.263	1.12-1.43	1.235	1.11-1.38
Unknown	212	1.085	0.94-1.26	0.979	0.80-1.19	1.260	1.01-1.57
Prior MDS[1]							
No (ref)	4096						
Yes	676	1.188	1.09-1.29	1.188	1.06-1.34	1.195	1.06-1.35
PPI[2]							
No (ref)	4408						
Yes	364	1.156	1.03-1.30	1.206	1.00-1.45	1.162	0.99-1.36
NCI Co-morbidity Score							
0 (ref)	2553						
1	1234	1.144	1.06-1.23	1.168	1.06-1.29	1.122	1.00-1.25
2	522	1.189	1.07-1.32	1.201	1.04-1.38	1.172	1.01-1.36
≥3	463	1.408	1.26-1.57	1.448	1.24-1.69	1.386	1.18-1.62

Abbreviations: NCI: National Cancer Institute; MDS: Prior Myelodysplastic Syndrome; PPI: Poor Performance Indicators.

[1]Patients with a Prior Myelodysplastic Syndrome (MDS) or myeloproliferative disease was identified from Medicare claims and was used as a proxy for high risk patients in the absence of disease stage.

[2]Poor Performance Indicators (PPI) were identified from Medicare claims and include the use of oxygen and related respiratory therapy supplies, wheelchair and supplies, home health agency services, and skilled nursing facility services that occurred 12 months prior to AML diagnosis.

[a]Model also includes geographic region, income and year of diagnosis.

however the information generated are complementary to findings from RCTs as clinical trial participants are subject to more controlled environments and are potentially not representative of individuals in the real-world. Therefore, there SEER-Medicare database is an invaluable tool to examine therapeutic strategies in actual practice settings among patients who have been historically underrepresented in clinical trials. With over 11,000 patients, it is one of the largest samples of AML patients with diverse geographic representation in the US. The SEER program is considered the gold standard in cancer surveillance and the linkage of claims based data from Medicare reduces the likelihood of treatment misclassification. However, with insurance claims data, we cannot determine physician's intent, equal access to medical care, or be able to capture treatments paid out of pocket. Furthermore, for a significant amount (68%) of the treated cohort, we were unable to define the type of chemotherapy received due to the highly toxic nature of conventional chemotherapy

treatments [29] for AML which requires urgent initiation of therapy in the inpatient setting. Inpatient admissions are paid out my Medicare based on ICD-9 diagnosis or procedures codes only and not on the chemotherapy J code administered. For a comprehensive examination of the comparative effectiveness of all anti-leukemic therapy, we included the patients who received Unknown therapy as a separate group. Finally, we cannot exclude the possibility of residual confounding in examining prognostic factors due to the absence of cytogenetic risk status and performance status in the dataset. We used Medicare claims to identify patients with a prior MDS and used this as a marker of disease severity, and also used Medicare claims to identify several indictors of poor performance. Performance status and disease severity influence clinicians' decisions to treat or the specific regimen to administer and these proxy variables may not adequately assess risk status or physical fitness for all patients in our study.

In conclusion, the findings from this study provide a rationale to strongly consider therapy rather than best supportive care in older patients who do not fit the criteria for more intensive regimens. While there are challenges in treating elderly patients with AML, these results indicate that age alone should not disqualify a patient from receiving intensive induction chemotherapy if they have favorable prognostic characteristics. Following the recent approval of BCL-2 inhibitors in combination with HMAs or low-dose intensive therapy, our results will serve as an important historical control for incidence of treated patients and their survival outcomes in this fragile cohort of AML patients.

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