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IMPROVING OUTCOMES FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA IN FIRST RELAPSE: A SINGLE CENTER EXPERIENCE

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Abstract

Background—The outcome of patients with relapsed acute myeloid leukemia (AML) remains unsatisfactory, with few available effective therapies. Increased understanding of the biology of the disease has led to the identification of novel therapeutic agents, several of which have been evaluated in recently conducted clinical trials.

Methods—We sought to determine whether the introduction of these agents as well as modern supportive care measures has already translated to better outcomes. We examined the outcomes of 1,056 patients with AML in first relapse treated between January 1993 and December 2013 at our institution.

Results—As previously reported, the independent prognostic factors for survival after first relapse, included age at relapse, cytogenetics, and duration of first complete remission (CR).

Conclusion—Upon multivariable analysis, treatment era was an independent predictor of survival, with significant improvement in overall survival between 2008–2013 as compared to prior time periods. Modern supportive care measures as well as participation in clinical trials of novel agents are already improving the outcomes in first relapse.

Keywords

acute myeloid leukemia; AML; relapse; outcomes

INTRODUCTION

Outcomes for most patients with acute myeloid leukemia (AML) remain poor.¹ In particular, outcomes for patients with AML who experience relapse are unsatisfactory, in general.² Although, approximately 60–80% of patients with AML achieve complete remission (CR), the majority will relapse, with the likelihood of attaining second or subsequent CR

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progressively diminished.³ Estey et al demonstrated that in patients with initial CR duration less than one year, the type of therapy received did not affect the overall outcome/survival; however, if the initial CR duration was greater than one year, there was a significant difference favoring those who received high dose cytarabine (HiDAC) containing regimens.⁴ At the extreme are patients who are refractory to their induction treatment who have a particularly dismal long-term prognosis.⁵ In this study we explored whether the introduction of modern supportive measures as well as novel non-myelosuppressive salvage strategies in the recent decade has translated to any improvements in the outcome.

METHODS

We reviewed the clinical data for all patients with AML who achieved CR at our institution from 1993–2013. Among 1,857 patients, 1,056 (57%) patients with available data on first relapse were identified during the study period. All patients signed consent forms for participation in research as approved by the Institutional Review Board of the University of Texas – MD Anderson Cancer Center. Four distinct time periods (treatment eras) were selected for comparison: 1993–1997, 1998–2002, 2003–2007, and 2008–2013. Demographic and clinical characteristics of the patients were examined and compared to determine predictors of long term outcome. Survival outcomes were evaluated using the Kaplan-Meier analysis and differences were compared using the log-rank test. Differences between cohorts were evaluated using the χ^2 test for nominal variables and the Mann-Whitney U test and Fisher exact test for continuous values. Variables with a p-value ≤ 0.10 were included in a multivariate analysis.

RESULTS AND DISCUSSION

Table 1 shows the baseline demographics of the study population. The median age for the overall group (n=1,056) was 60 years (range 15–86 years). There were significant differences in terms of treatment era for median age at relapse (58 years in 1993–1997, 60 years in 1998–2002, 58 years in 2003–2007, and 62 years in 2008–2013, p -value 0.04) with the more recent cohort having an older population. There was a significant difference in terms of number of patients receiving allogeneic stem cell transplantation (SCT) in first CR (CR1) by treatment era (3 in 1993–1997, 8 in 1998–2002, 23 in 2003–2007, 41 in 2008–2013, p -value <0.001); Although there was no significant difference in terms of outcomes between the two groups with or without SCT in CR1 (p -value 0.55, Table 1b), it should be noted that the number of patients who underwent SCT in CR1 was small (6.8% of the cohort)

Predictors of survival at the time of first relapse

Factors significant for predicting differences in survival included: age >65 years at relapse, AML subtype by FAB classification, secondary compared to de novo AML, treatment era, adverse cytogenetics, and CR1 duration greater or less than 12 months. These are, in general, confirmatory of relevant factors reported by other studies.⁶

Multivariate analysis of predictors of survival at first relapse

Significant variables (p -value < 0.10) identified in the univariate analysis were included in a multivariate analysis. Age >65 years at relapse; FAB morphological diagnoses of acute myelomonocytic leukemia, acute monocytic leukemia, and acute erythroid leukemia; as well as intermediate and adverse-risk cytogenetics, duration of CR1, and the era of treatment were independent predictors of survival after relapse. Survival was significantly better for patients relapsing in the era 2003–2013 compared to those relapsing 1993–2003 (6.3 months versus 5.3 months, p -value 0.004). (Figure 1a) Compared to patients relapsing between 2008–2013, patients relapsing between 1998–2002 and 1993–1997 had a survival disadvantage of 30% (HR 1.297; 95% CI= 1.076–1.564) and 50% (HR 1.505; 95% CI= 1.214–1.866), respectively. The difference with the 2003–2007 treatment era was not statistically significant. Figure 1b demonstrates survival differences by the treatment era when divided into 5-year intervals.

We then performed multivariate analysis using Cox proportional hazard regression in the subgroup of patients treated with HiDAC-based therapy, which was the most frequently used therapy given throughout all of the treatment eras. The variables included were the same as the previous multivariate analysis. Importantly, this model confirmed the results of the previous analysis and found that compared to patients relapsing between 2008–2013, patients relapsing between 1998–2002 and 1993–1997 had a survival disadvantage of 33% (HR=1.332; 95% CI= 1.071–1.657) and 57% (HR=1.566; 95% CI= 1.229–1.995), respectively. Again, the difference with the 2003–2007 treatment era was not statistically significant.

Breems et al⁶, studied outcomes in 1,540 patients with AML from HOVON/SAKK clinical trials from 1987–2001. Among 1108 who achieved CR, 667(60%) relapsed. They reported four independent predictors of overall survival after first relapse including unfavorable cytogenetics at diagnosis, duration of first CR, older age, and prior history of SCT. Similarly, Kurosawa et al examined the outcomes of patients in first relapse at their institution.⁷ Among 1,535 patients with AML who achieved CR, 1,015 (66%) relapsed, with about a half achieving a second CR (CR2). On multivariate analysis, duration of CR1 of one year or greater, achievement of CR2, and SCT as salvage therapy were independent predictors of survival. The authors concluded that attaining CR2 followed by the ability to undergo SCT represented the best chance of achieving long term survival.

Our results are consistent with prior analyses of patients with AML in first relapse, with age, cytogenetics and duration of CR1 as important predictors of survival in first relapse. In our study, the outcomes of patients who underwent SCT in CR1 was not significantly different from those who did not. However, it is important to note that the number of patients who underwent SCT in CR1 was small (6.8% of the cohort) thereby making this analysis limited in value. Importantly, we noted that era of treatment is an important predictor suggesting that more modern strategies of therapy as well as supportive care may already be impacting the outcomes of these patients. Of interest, this improvement in the more recent era could not be attributed to the patient characteristics. In fact, patients treated in the more recent era

were significantly older, with no difference in the proportion of patients with adverse cytogenetics.

Several underlying factors may be responsible for the improvement in outcomes. First, limiting the more intensive chemotherapy-based induction regimens to the younger population is associated with less toxicity and the ability to tolerate subsequent salvage strategies.⁸ Our group has previously reported that, in patients with newly diagnosed AML, aged 65 years or older, treatment with hypomethylating agents is associated with similar outcomes compared to intensive chemotherapy.⁹ In that analysis of 671 patients treated between years 2000 and 2010 (with either hypomethylating agents or the more traditional intensive cytotoxic chemotherapy), there was no statistically significant difference in either the 2-year relapse free survival rates or the median overall survival between the two groups, suggesting that treatment with hypomethylating agents is associated with similar long term outcomes as intensive chemotherapy. Second, a number of novel targeted therapies have been introduced that may potentially be having positive influence on the outcomes, especially in older patients. For example, the availability of clinical trials of fms-like tyrosine kinase-3 (FLT3) inhibitors may be the reason for an improved outcome in the specific population of patients with mutated *FLT3*.¹⁰ Takahashi et al. recently reported that among 120 patients with AML and *FLT3* internal tandem duplication (*FLT3*-ITD) mutation, there was a statistically significant improvement in OS for the patients with primary refractory disease or CR1 duration less than 12 months who were treated with FLT3 inhibitors. Importantly, on multivariate analysis, the use of FLT3 inhibitors in patients with *FLT3*-ITD mutation, was an independent predictor for improved OS.¹⁰ Found in approximately 25% of patients with AML, *FLT3*-ITD serves not only as a marker of poor prognosis, but also a potential drug target with several clinical trials of agents targeting this kinase, underway.^{11–13} Reports of single agent activity¹⁰ as well as combination of FLT3 inhibitors with other agents in the salvage setting^{10,14} have been promising. Third, the introduction of the hypomethylating agents decitabine^{15,16} and azacytidine^{17,18,19} have provided us with less toxic strategies for treating older, infirm patients both in the frontline and salvage settings.^{14,20}

In summary, despite patients with AML presenting at an older age at diagnosis and relapse, we have shown that the outcomes of patients with AML in first relapse have improved over time, and that the era of therapy is an independent prognostic factors for overall survival after first relapse with an improved survival in the last several years.

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Figure 1.

a: Overall Survival, by Earliest and Most Recent Treatment Era
 b: Overall Survival, by Treatment Era

Table 1

a: Characteristics of patients with relapsed AML	
Characteristics	N=1056 (range or %)
Age, median (range)	60 (15 – 86)
Male	572 (54.2)
De novo or secondary AML	
De novo	852 (80.7)
Secondary	204 (19.3)
Period when relapse occurred	
1993–1997	181 (17.1)
1998–2002	286 (27.1)
2003–2007	268 (25.4)
2008–2013	321 (30.4)
Cytogenetic	
Favorable	74 (7)
Intermediate	652 (61.7)
Adverse	259 (24.5)
IM/ND**	71 (6.7)
Therapy received***	
HDAC	860 (81.4)
HMA	52 (4.9)
Targeted	43 (4.1)
Other/combinations	1031 (97.6)
Type of response before relapse	
Complete	986 (93.4)
Complete without platelet recovery	70 (6.6)
Stem cell transplant in CR1	
Yes	72 (6.8)
No	984 (93.2)
Duration of CR1 in months, median (range)	8 (0.3 – 144.4)
Median survival after relapse, months (95% CI)	5.85 (5.38 – 6.32)

a: Characteristics of patients with relapsed AML					
Characteristics	N=1056 (range or %)				
Median follow up after relapse, months (95% CI)	****	58.8 (50.7 – 67)			
b: Univariate Analysis of Predictors of Survival					
Characteristics	N=1056 (%)	Events (%)	Median OS (months)	95% CI	p-value
Age at relapse					.001
65 years	685 (65)	587 (86)	6.6	5.95 – 7.25	
>65 years	371 (35)	332 (90)	4.2	3.50 – 4.98	
Diagnosis*					.004
AML	703 (67)	612 (87)	6.1	5.56 – 6.65	
AMML	196 (19)	167 (85)	6.1	4.95 – 7.33	
AMOL	92 (9)	80 (87)	3.4	1.94 – 4.96	
AEL	46 (4.4)	42 (91.3)	5.0	2.31 – 7.75	
Mega	19 (1.8)	18 (94.7)	3.9	0 – 8.43	
De novo or secondary AML					.001
De novo	852 (80.6)	732 (85.9)	6.2	5.60 – 6.76	
Secondary	204 (19.4)	187 (91.7)	4.9	3.97 – 6	
Period when relapse occurred					.006
1993 – 1997	181 (17.1)	176 (97.2)	4.8	3.91 – 5.69	
1998 – 2002	286 (27.1)	268 (93.7)	5.7	4.55 – 6.81	
2003 – 2007	268 (25.4)	241 (89.9)	6.0	5.19 – 6.90	
2008 – 2013	321 (30.4)	234 (72.8)	6.7	5.86 – 7.61	
Cytogenetics					.001
Favorable	74 (7)	53 (71.6)	13.9	10.52 – 17.28	
Intermediate	652 (61.7)	555 (85.1)	6.6	5.89 – 7.25	
Adverse	259 (24.5)	249 (96.1)	3.4	2.89 – 3.95	
IM/ND**	71 (6.7)	62 (87.3)	5.3	3.15 – 7.43	
Therapy received***					
HDAC	860 (81.4)	757 (88)	6.08	5.52 – 6.64	.05

.05

b: Univariate Analysis of Predictors of Survival					
Characteristics	N=1056 (%)	Events (%)	Median OS (months)	95% CI	p-value
No HDAC	196 (18.6)	162 (82.6)	5.06	4.10 – 6.02	
HMA	53 (5)	46 (86.8)	3.45	2.08 – 4.82	.007
No HMA	1004 (95)	873 (86.9)	5.98	5.50 – 6.46	
Targeted	43 (4.1)	30 (69.8)	9.59	4.86 – 14.32	.002
No Targeted	1013 (95.9)	889 (87.7)	5.75	5.26 – 6.24	
Other/combination	1031 (97.6)	898 (87.1)	5.88	5.41 – 6.35	.28
No Other	25 (2.4)	21 (84)	4.37	1.66 – 7.08	
Type of response before relapse					.05
Complete	986 (93.4)	860 (87.2)	6.05	5.57 – 6.53	
Complete without platelet recovery	70 (6.6)	59 (84.3)	4.37	3.20 – 5.54	
Stem cell transplant in CR1					0.55
No	984 (93.2)	862 (87.6)	5.9	5.41 – 6.35	
Yes	72 (6.8)	57 (79.2)	5.2	3.40 – 6.99	
Duration of CR1					0.001
<=8 months	540 (51.1)	499 (92.4)	3.9	3.54 – 4.42	
>8 months	516 (48.9)	420 (81.4)	9.3	7.88 – 10.77	

c: Multivariate Analysis of Predictors of Survival			
Characteristics	p-value	HR	95% CI
Age at relapse	0.01	1.02	1.01–1.02
Diagnosis*			
AML (reference)		1.00	
AMML	0.19	1.13	0.94–1.36
AMOL	0.01	1.60	1.25–2.04
AEL	0.41	0.87	0.63–1.21
Mega	0.20	1.51	0.80–2.84
Period when relapse occurred	0.01		
1993–1997	0.01	1.51	1.21–1.87
1998–2002	0.01	1.30	1.08–1.56
2003–2007	0.30	1.10	0.92–1.33

c: Multivariate Analysis of Predictors of Survival				
Characteristics	p-value	HR	95% CI	
2008–2013 (reference)		1.00		
Cytogenetics	0.01			
Favorable (reference)		1.00		
Intermediate	0.05	1.34	0.10–1.81	
Adverse	0.01	2.28	1.64–3.16	
Duration of CR1	0.01	0.98	0.97–0.98	

Abbreviations

* FAB=French American British AML classification

** IM/ND=insufficient metaphase/not done

*** Treatment types are not mutually exclusive, HiDAC=high dose cytarabine (ARA-C), HMA=hypomethylating agent

***** Reverse Kaplan-Meier analysis

Abbreviations

* Diagnosis type: AML=acute myeloid leukemia, other, AMML=acute myelomonocytic leukemia, AMOL=acute erythroid leukemia, AEL=acute erythroid leukemia, Mega=acute megakaryocytic leukemia

** IM/ND=insufficient metaphase/not done

*** Treatment types are not mutually exclusive, HiDAC=high dose cytarabine (ARA-C), HMA=hypomethylating agent

Abbreviations

* Diagnosis type: AML=acute myeloid leukemia, other, AMML=acute myelomonocytic leukemia, AMOL=acute erythroid leukemia, AEL=acute erythroid leukemia, Mega=acute megakaryocytic leukemia