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Smoking Adversely Affects Survival in Acute Myeloid Leukemia Patients

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Summary

Smoking adversely affects hematopoietic stem cell transplantation outcome. We asked whether smoking affected outcome of newly diagnosed acute myeloid leukemia (AML) patients treated with chemotherapy. Data were collected on 280 AML patients treated with high-dose cytarabine and idarubicin-containing regimens at Roswell Park Cancer Institute who had smoking status data at diagnosis. Patients' gender, age, AML presentation (*de novo vs.* secondary), white blood cell (WBC) count at diagnosis, karyotype and smoking status (never *vs.* ever) were analyzed. Among the 161 males and 119 females with a median follow-up of 12.9 months, 101 (36.1%) had never smoked and 179 (63.9%) were ever smokers. The proportion of patients between never and ever smokers was similar with respect to age, AML presentation, WBC count at diagnosis or karyotype based on univariate analysis of these categorical variables. Never smokers had a significantly longer overall survival (60.32 months) compared to ever smokers (30.89; p=0.005). In multivariate analysis incorporating gender, age, AML presentation, WBC count, karyotype, and smoking status as covariates, age, karyotype and smoking status retained prognostic value for overall survival. In summary, cigarette smoking has a deleterious effect on overall survival in AML.

Introduction

Tobacco use is the single most preventable cause of disease, disability and death in the United States. According to Centers for Disease Control and Prevention,[1] each year an

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estimated 443,000 people die prematurely from smoking or exposure to secondhand smoke, and another 8.6 million have a serious illness caused by smoking. Approximately 43.4 million U.S. adults smoke cigarettes. On average, adults who smoke cigarettes die 14 years earlier than nonsmokers. Coupled with this enormous health toll is the significant economic burden of tobacco use—more than $96 billion per year in medical expenditures and another $97 billion per year resulting from lost productivity.

Since smoking was shown to adversely affect outcome following hematopoietic stem cell transplantation (HSCT),[2, 3] we asked whether smoking has a similar effect on AML patients treated with chemotherapy.

Methods

Patients

Three hundred and twenty seven newly diagnosed AML patients between June 1990 and December 2008 were treated at Roswell Park Cancer Institute (RPCI) with high-dose cytarabine and idarubicin-containing induction regimens. The medical records of these patients were reviewed and data were collected on the patients' gender, age (<60 and ≥60 years old), AML presentation [*de novo vs.* secondary (both therapy-related and antecedent hematologic disorder)], white blood cell (WBC) count at diagnosis (recorded as $<100 \times 10^9$/L *vs.* $\geq 100 \times 10^9$/L and as continuous variable), karyotype [favorable, intermediate, unfavorable, and unknown[4]] and smoking status (never smokers *vs.* former and current). Smoking information was obtained from the physician's initial note and was available on 280 patients. The analysis was approved by RPCI's Scientific Review Committee and Institutional Review Board.

Treatment

Induction chemotherapy consisted of high-dose cytarabine [3 gm/m^2 (1.5 mg/m^2 for age ≥50) every 12 hrs × 12 doses] and idarubicin (12 mg/m^2 × 3 doses), and 62 of 280 patients received priming with arsenic trioxide (0.15 mg/kg to 0.65 mg/kg) prior to high-dose cytarabine and idarubicin on a phase I clinical trial. Consolidation therapy varied over time. Of note, 34 patients underwent an allogeneic HSCT in first remission.

Statistical Analyses

Descriptive statistics and chi-square tests were used to explore the univariate associations between the dependent and independent variables. Data were not censored at the time of allogeneic transplantation, but multivariate modeling that included and excluded these patients had similar results. Kaplan-Meier analyses were done to assess univariate differences in mean overall survival (OS) and progression-free survival (PFS) of various characteristics. PFS was defined as the time between achievement of complete remission (CR) and either the date of relapse or, among patients who did not relapse, the date of last follow-up.[5] The Log Rank (Mantel-Cox) test within Kaplan-Meier analysis was used to test for differences in the survival distributions for the factor levels of each covariate. Additionally, this was repeated after adjusting for individual smoking status (never vs. ever smokers) within Kaplan-Meier.

Pulmonary and cardiac toxicities, infection, and multi-organ failure toxicities were obtained from medical records and were categorized according to the common terminology criteria for adverse events v. 3. Further, patients were categorized as having no toxicity or at least mild toxicity in any of the preceding areas. Differences in toxicity levels were assessed using chi-square analysis.

Cox Proportional Hazard Modeling was used to assess prognostic factors of OS and PFS and was limited to patients for whom complete data for all variables in the model were available (OS: n=266, PFS: n=181). Tests for interactions between variables of interest and smoking status were performed using Cox Proportional Hazard Modeling for both OS and PFS outcomes.

OS (Figure 1A) and PFS (Figure 1B) plots were obtained from Cox proportional hazard models adjusted for age (<60 years vs. ≥ 60 years), gender (female, male), AML presentation (*de novo* vs. secondary), WBC count at diagnosis ($<100 \times 10^9$/L vs. $\geq 100 \times 10^9$/L), and karyotype (intermediate, unfavorable, favorable, and unknown). All models were stratified by participant smoking status at diagnosis (never, previous, or current smokers). Figure 1A (OS) was analyzed among 266 patients, including 207 events and 59 censors; Figure 1B (PFS) was analyzed among 179 patients and included 130 events and 49 censors. Survival curves were generated by fixing at the mean of each covariate included in the model. All significance testing was based upon a p-value of <0.05. Analyses were completed using SPSS version 14.0.

Results

Patient Characteristics

Patient characteristics are summarized in Table 1. The median age of the whole cohort was 56 (range 18–85) years. The median follow-up was 12.9 (range, <1-+195) months. Among the 81 patients with secondary AML, 50 had antecedent hematologic disorders and 31 had therapy-related AML; due to the small numbers, they were analyzed together. There were more males among ever smokers (p=0.045). Ever smokers consisted of 117 former smokers and 62 current smokers.

Univariate Analysis

Based on univariate analyses, there were no significant differences in the distribution of age, period of accrual, AML presentation, WBC count at diagnosis or karyotype between smoking status strata (Table 1). Never and ever smokers had similar CR rates (never: 64.4% *vs.* ever: 63.1%; p=0.897) and there was no difference in achievement of CR between former (60.2%) and current (68.9%) smokers (p=0.327), based on chi square analysis. Table 2 shows the distribution of the consolidation treatments received among the total population, among never smokers, and among ever smokers. Based on chi square analyses, there was no statistically significant difference between the distribution of consolidation treatments received between never and ever smokers (see footnote, Table 2). Finally, there were no statistically significant differences in incidence of pulmonary, cardiac, or infection toxicities (none vs. any) between never and ever smokers based on chi square analysis (Supplemental Table 1).

OS for the Whole Cohort by Selected Characteristics

OS[6] for the whole cohort by selected characteristics is summarized in Table 3 based on univariate Kaplan-Meier analysis. Among the 280 patients with known smoking status, the mean OS time was 45.24 months [95% CI: 37.11 to 53.38 months] with 59 censored patients. Never smokers had a significantly longer OS time [60.32 months (44.95–75.69)] compared to ever smokers [30.89 months (27.73–46.05)] (p=0.005). Age ≥60 and secondary AML were associated with shorter mean survival time (p<0.001 for both age and AML presentation). Patients with favorable karyotype (mean OS: 114.97 months) survived longer than patients with intermediate (51.43 months) or unfavorable karyotypes (30.35 months) (p<0.001).

OS within Smoking Strata for Selected Characteristics

After stratification by smoking status (ever vs. never), similar patterns in survival distributions existed within factor levels (categories) of each covariate. Generally, ever smokers had shorter OS compared to never smokers. Among ever smokers only (n=179), current smokers at diagnosis had longer OS than previous smokers (52.32 vs. 28.75 months), but this difference was not statistically significant (p=0.064; data not shown). In multivariate Cox Proportional Hazard Modeling of ever smokers (n=168 total, previous: n=109, current: n=59), after adjusting for covariates, it appears that current smokers have a lower probability of survival compared to previous smokers (HR=0.833, 95% CI: 0.588-1.244), but this was not statistically significant (p=0.373).

In stratified analysis by each karyotype, smoking was only significantly associated with decreased OS among patients in the unfavorable karyotype cohort (p=0.007; Table 3). Additionally, after stratification by each age group (<60 years, ≥60 years), smoking significantly decreased survival among younger patients (never: 80.6 vs. ever: 56.1 months, p=0.015) but had no statistically significant effect among patients ≥60 years (32.6 vs. 16.6 months, p=0.091).

PFS for the Whole Cohort by Selected Characteristics

Similarly, there was a significant difference of PFS between never smokers (65.26 months; 95% CI: 45.05–85.48) and ever smokers (43.01 months; 95% CI: 29.97–56.04; p=0.020), but there were no significant differences in PFS between former and current smokers (33.48 vs. 58.018 months, p=0.208). Significant differences in PFS were also observed among the whole sample by age, karyotype, and AML presentation (Supplemental Table 2).

PFS within Smoking Strata for of Selected Characteristics

Among never smokers only (n=66) there were no differences in factor levels of karyotype (p=0.368) and AML presentation (p=0.185) on PFS. However, these differences still existed among ever smokers (Supplemental Table 2).

In stratified analyses by each karyotype category, ever smoking was only statistically associated with shorter PFS among patients with unfavorable karyotypes (p=0.006; Supplemental Table 2). In contrast to OS, analysis stratified by age did not result in a statistically significant difference in PFS with smoking status in younger patients. After stratification by AML presentation, ever smoking significantly decreased PFS in patients with *de novo* presentation only (p=0.042).

Out of all 327 patients initially considered for the present study, complete data for all variables of interest were available for 266 patients. The majority of missing data were due to patients' unknown smoking status and unavailable cytogenetic data. Kaplan-Meier analysis of these 61 patients showed decreased OS compared to data of the 266 patients with complete data [25.45 months (12.41–38.48) vs. 47.17 months (38.68–55.66), p=0.001] (data not shown).

Multivariate Analysis

Multivariate analysis was performed using age, AML presentation, WBC count, karyotype, and smoking status as covariates. Compared to patients <60 years old, those ≥60 years of age were nearly two times more likely to die (HR=1.962) after adjusting for all other covariates. Additionally, ever smokers were about 64% more likely to have an event (death) (HR=1.637). After adjusting for all other covariates, unfavorable karyotype (HR=2.049) was associated with worse survival, while favorable karyotype (HR=0.475) was associated with improved survival compared to those with intermediate karyotypes. There were no

differences in death among those with an unknown karyotype compared to those with intermediate karyotypes. Additionally, no differences were present in gender or AML presentation. Furthermore, after adjusting for gender, age, karyotype, WBC count at diagnosis, AML presentation, and smoking status, there was no statistically significant association with decade of diagnosis and survival (HR=0.860, 95% CI: 0.625–1.184 [p=0.355]). Additionally, there was no statistically significant interaction between smoking status and decade of diagnosis on OS (p for interaction = 0.492). Finally, no interactions between covariates of interest and ever smoking were observed in multivariate models of OS (Table 4 and Figure 1A).

To analyze the effect of transplantation, excluding the 34 transplanted patients resulted in a HR of 1.442 (95% CI: 1.047–1.988) for ever smokers compared to never smokers after adjusting for all other covariates. When these patients were included in the model, ever smokers has a hazard ratio of 1.637 (95% CI: 1.212–2.211). Therefore, transplantation status did not substantially alter the relationship we observed between smoking status and risk of death in this patient cohort.

Using PFS as the outcome of interest, ever smokers were about 70% more likely to die compared to never smokers (HR=1.722) after adjusting for other covariates (Supplemental Table 3, Figure 1B). Age >60 years and unfavorable karyotype were also associated with increased risk. No statistically significant interactions between smoking status (ever vs. never) and any covariates on PFS were present (Supplemental Table 3).

Discussion

Our data demonstrate deleterious effect of smoking on AML outcome. In a previous study[7] of 643 newly diagnosed AML patients, smokers had significantly higher rate of pulmonary infection during induction chemotherapy, shorter disease-free and OS. Similar to our study, cigarette smoking worsened the poor OS in patients with unfavorable karyotype, but did not significantly influence the prognosis of other karyotype risk groups. This can be explained by the chemicals found in tobacco smoke that were shown to cause aberrations in chromosomes 5[8], 7[9, 10] and 8[8, 11, 12] which have been linked to adverse outcome following AML treatment.[13] Finally, of note is the fact that the difference in OS of never smokers with intermediate vs. unfavorable karyotypes was less pronounced than among ever smokers, again substantiating the deleterious effect of tobacco smoke especially among patients with unfavorable karyotype.

In addition, both studies demonstrated equal distribution of secondary AML among smokers and non-smokers and similarly worse outcome for secondary AML unrelated to smoking status. However, in that study it should be noted that smoking did not have an independent prognostic effect in multivariate analysis. Also similar to this previous study, smoking was associated with shorter OS, but did not significantly influence OS in patients who were ≥60 years old, most probably due to their overall poor outcome. However, in contrast to that study, we did not detect increase in pulmonary infections or other adverse events in ever vs. never smokers. Possible explanations for the differences between the two studies are the cohorts' size and different treatment regimens; the previous study used a variety of treatment protocols while the current work only included similar induction regimen for all patients.

An association between smoking and cancer outcome is not unique to leukemia. For example, at least two groups reported a close association between smoking and adverse lung cancer outcome. Sakao et al[14] studied the impact of smoking on the prognosis of 121 patients with adenocarcinoma of the lung. Their results showed poorer outcome among smokers. Similarly, Tsao et al[15] analyzed the outcome of 1370 lung cancer patients and

demonstrated a better outcome for non-smokers. In addition, smoking was associated with increased odds of lung metastasis from esophageal cancer and this relationship was site-specific.[16] Finally, the influence of smoking on outcome after radiochemotherapy for anal cancer was studied among 68 patients.[17] There was a significant difference in local control between smokers and non-smokers (smokers 74% vs. non-smokers 91%; p=.03).

Previous studies have demonstrated a modest association between smoking and incidence of leukemia, particularly for myeloid disorders. Based on these studies, the 2004 Surgeon General's Reports added myeloid leukemia to the ever-expanding spectrum of disorders that are increased with smoking.[18] The exact link between smoking and leukemia has not been elucidated. One of the causes could be the benzene content in tobacco smoke, although there could also be other chemicals involved. Metabolites of benzene are responsible for causing DNA damage and impairing DNA repair in hematopoietic cells in the marrow.[19] Therefore, in addition to its causative role, benzene from cigarettes may also adversely affect normal hematopoietic cells and lead to delayed count recovery resulting in increased toxicities. Another possibility is a relationship between genetic variability, susceptibility to leukemia and modulating the effect of chemotherapeutic agents. This is supported by the presence of known functional polymorphisms of genes encoding proteins associated with processing carcinogens in lung cancer. For example, the excision repair cross-complementation group 1 (*ERCC1*) gene plays a pivotal role in DNA repair and has been linked to protection against carcinogenesis and resistance to platinum-based anticancer drugs in lung cancer.[20, 21] Further, it was recently shown that functional single-nucleotide polymorphisms in *ERCC1* are associated with an increased susceptibility to lung cancer, alone and as a gene-smoking joint effect.[22] Interestingly, the same gene was recently shown to be associated with increased lung and metabolic toxicities in similarly-treated AML patients.[23] This latter publication did not analyze the patients' smoking status. Therefore, studying single-nucleotide gene polymorphism, smoking status and treatment outcome is warranted in AML.

In a study published by our group earlier,[24] we had shown that leukemia mortality has decreased overall in the United States in parallel with decreased smoking. Analyzed on a state-specific basis, leukemia mortality has decreased in states where smoking rates declined markedly but remained unchanged where smoking prevalences were relatively stable suggesting that declining rates of leukemia mortality are associated with changing patterns of smoking behavior. Interestingly, even though overall smoking incidence decreased in New York state,[1] this was not the trend in our patient population suggesting that the Western part of the state might be different in its smoking cession incidence. While this was an ecological correlational analysis, the current study is a retrospective analysis of similarly treated patients of the impact of smoking and outcome in patients with AML. Therefore, the current study supports our previous observation.

One of the limitations of this study is that we do not have detailed data on smoking history, such as smoking pack-years. Hence we could not determine whether the mortality is higher among heavy smokers compared to other groups. However, current and former smokers were combined in this analysis in order to assess the effect of any smoking on prognostic factors. More information on smoking history such as when previous smokers actually quit, years smoked, cumulative pack years etc may be needed to understand this relationship. However, one of the caveats of smoking histories is that they are subjective, i.e., collected from the patients. The medical history, trying to quantitate the current mean daily cigarette consumption (consumption rate), the cumulative risk (pack years) and the various types of smoking, including inhalation habits, may not be accurate because smokers may underrate their tobacco consumption.[25] Additionally, current and previous smokers may recall their smoking behaviors differently. A more accurate quantification method of current nicotine exposure is the measurement of cotinine (as surrogate for nicotine) levels in the serum. We

propose that future trials consider using cotinine as a method to assess current nicotine (tobacco) exposure among smokers as well as recent secondhand smoke exposure among non-smokers. While this study is a correlational analysis and does not in itself imply a causal relationship between smoking and AML mortality, there is a biologic basis that suggests that this relationship is plausible.

Another caveat of this study is its retrospective design, and the need to collect data, including smoking status at diagnosis, from physician notes within each patient's medical chart. Further, there were 47 patients on whom we did not have smoking history and who had a relatively poor outcome. We propose that their poor outcome may be related to treatment period, as 46 of these patients were treated between 1990 and 1998, whereas only one patient was treated after 1998. However, diagnosis time period itself (diagnosed 1990–1998, diagnosed 1998–2008) was not related to AML outcome among the whole cohort (analysis not shown).

In conclusion, cigarette smoking pose a deleterious effect on OS and PFS in similarly treated AML patients. We propose to study genetic variability based on smoking status to better understand smoking's deleterious effect on AML outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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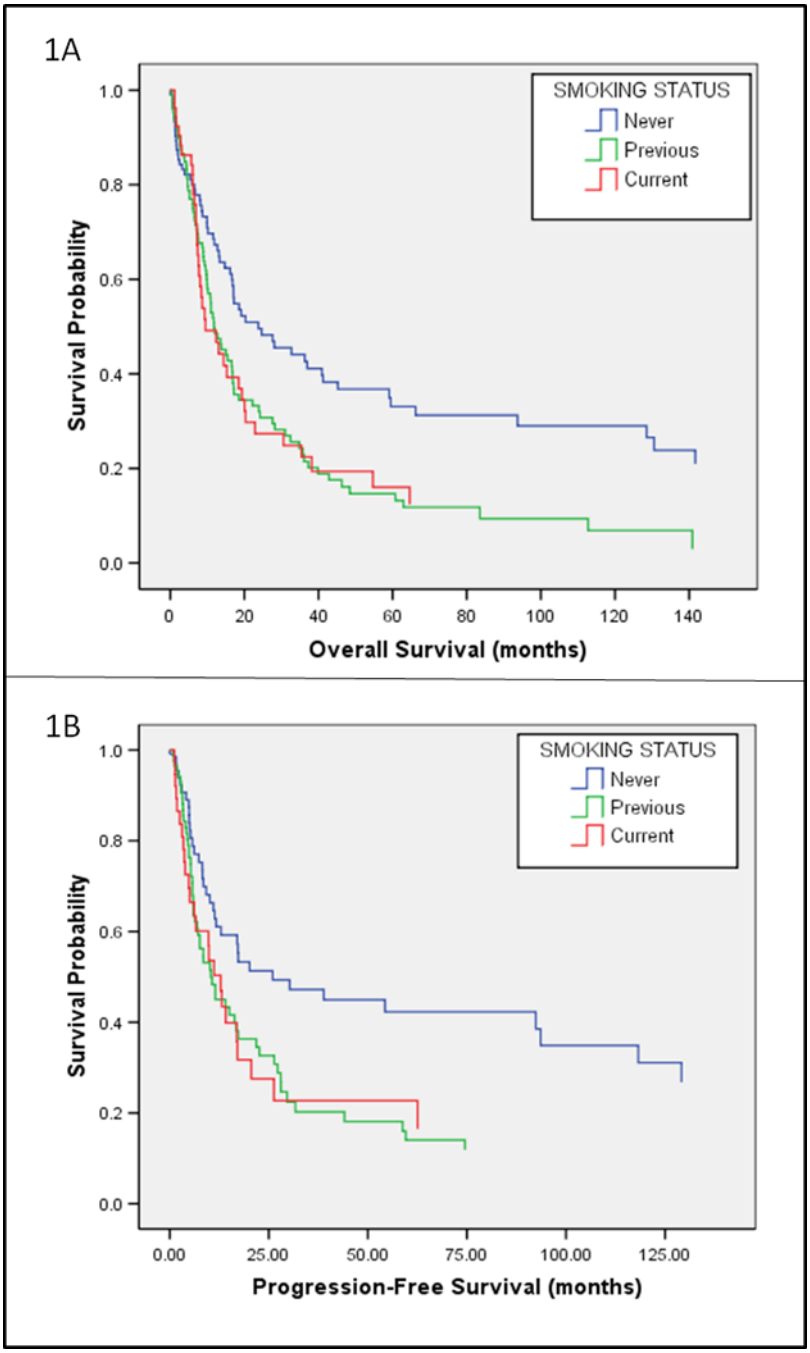

1. .

Overall and progression free survival of similarly-treated AML patients by smoking status. 1A: Overall Survival of 244 similarly-treated AML patients (188 events, 56 censored) by smoking status based obtained from Cox proportional hazard model. Cox proportional hazard model assessing overall survival was adjusted for gender, age, AML presentation (*de novo* vs. secondary), WBC count at diagnosis, and karyotypes (unfavorable, intermediate, favorable). Model and survival plot were stratified by patient smoking status. 1B: Progression-free survival of 164 patients (118 events, 46 censored) by smoking status obtained from Cox proportional hazard model. Cox proportional hazard model assessing progression-free survival was adjusted for gender, age, AML presentation (*de novo* vs.

secondary), WBC count at diagnosis, and karyotypes (unfavorable, intermediate, favorable). Model and survival plot were stratified by patient smoking status.

TABLE 1

Selected characteristics of the total study cohort and stratified by smoking status: never *vs.* ever smokers

Characteristic	Total 'N' (n=280)		Never Smokers (n=101)		Ever Smokers (n=179)		P
	N	%	N	%	N	%	
Sex							
Female	119	42.5	51	50.5	68	38.0	**0.045**
Male	161	57.5	50	49.5	111	62.0	
Age							
<60 years	160	57.1	59	58.4	101	56.4	0.802
≥60 years	120	42.9	42	41.6	78	43.6	
Period of Accrual							
1990–1997	147	52.5	51	50.5	96	53.6	0.621
1998–2008	133	47.5	50	49.5	83	46.4	
AML presentation							
De novo	201	71.8	76	75.2	125	69.8	0.407
Secondary	79	28.2	25	24.8	54	30.2	
WBC count							
$<100\times10^9$/L	250	89.3	88	87.1	162	90.5	0.423
$\geq100\times10^9$/L	30	10.7	13	12.9	17	9.5	
Karyotype* (n=266)							
Favorable	24	9.0	9	9.2	15	8.9	
Intermediate	119	44.1	45	45.9	74	44.0	0.989
Unfavorable	100	37.6	36	36.7	64	38.1	
Unknown	23	8.6	8	8.2	15	8.9	
Mortality							
Alive	59	21.1	30	29.7	29	16.2	**0.010**
Dead	221	78.9	71	70.3	150	83.8	

Abbreviations: AML, acute myeloid leukemia; N, number; WBC, white blood cell;

P-value based on chi square analysis, comparing never and ever smokers. Boldface P-values represent chi square analyses that are statistically significant at $p < 0.05$ level.

* Karyotype was unavailable for 14 individuals. Stratified Karyotype distributions are based on 98 never smokers and 168 ever smokers.

Table 2

Consolidation treatment regimens*

Treatment	Never Smokers	Ever Smokers	Total
VP/Cy-2.4	13 (19.4%)	17 (14.4%)	30 (16.2%)
VP/Cy-3.6	9 (13.4%)	20 (16.9%)	29 (15.7%)
BMT	9 (13.4%)	9 (7.6%)	18 (9.7%)
HiDAc ×4	6 (9.0%)	10 (8.5%)	16 (8.6%)
HiDAc/Ida	6 (9.0%)	7 (5.9%)	13 (7.0%)
HiDAc/Ida w/VP/Cy3.6	1 (1.5%)	11 (9.3%)	12 (6.5%)
HiDAc ×3	4 (6.0%)	7 (5.9%)	11 (5.9%)
HiDAc × 1 w/BMT	2 (3.0%)	5 (4.2%)	7 (3.8%)
HiDAc × 1	4 (6.0%)	3 (2.5%)	7 (3.8%)
VP/Cy-2.4 w/BMT	2 (3.0%)	3 (2.5%)	5 (2.7%)
Other†	4 (6.0%)	15 (12.7%)	19 (10.3%)
None	7 (10.4%)	11 (9.3%)	18 (9.7%)
Total	67 (100.0%)	118 (100.0%)	185 (100.0%)

Abbreviations: VP/Cy-2.4; etoposide 2.4 g/m^2 as continuous infusion over 34.3 hours and cyclophosphamide 50 mg/kg of ideal body weight over 2 hours daily for three days; VP/Cy-3.6; etoposide 3.6 g/m^2 as continuous infusion over 51.4 hours and cyclophosphamide 50 mg/kg of ideal body weight over 2 hours daily for four days; HiDAc, 3 gm/m^2 every 12 hours every other day for 6 doses; HiDAc/Ida, high-dose cytarabine [3 gm/m^2 (1.5 mg/m^2 for age ≥ 50) every 12 hrs × 12 doses] and idarubicin (12 mg/m^2 × 3 doses); BMT, allogeneic bone or marrow transplantation;

*Based on chi square analyses, there was no statistically significant differences in the distribution of consolidation treatments received between never smokers and ever smokers (p=0.481).

†Other, all cases with <5 patients/regimen;

Percentages depict distribution of treatments received by smoking status; percentages of "total" are out of n=185.

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Table 3

Mean overall survival for various characteristics based on Kaplan-Meier Analysis, stratified by smoking status (n=280)

	Mean Survival – Overall n=280*					Mean Survival – Never Smokers n=101					Mean Survival – Ever Smokers n=179					Never vs. Ever smokers
Characteristic	**N**	**N^c^**	**mths**	**95% CI**	**p**	**N**	**N^c^**	**mths**	**95% CI**	**p**	**N**	**N^c^**	**mths**	**95% CI**	**p**	**p**
Smoking Status																**n/a**
Never	101	30	60.3	45.0 – 75.7	**0.005**											
Current/Former	179	29	30.9	27.7 – 46.1												
Age																
<60 years	160	55	66.5	53.2 – 79.7	**<0.001**	59	27	80.6	58.8 – 102.5	**<0.001**	101	28	56.1	40.7 – 71.5	**<0.001**	**0.015**
≥60 years	120	4	22.6	15.8 – 29.4		42	3	32.7	17.0 – 48.3		78	1	16.6	11.5 – 21.8		0.091
Sex																
Female	119	31	52.5	38.8 – 66.2	0.168	51	14	56.2	34.9 – 77.5	0.419	68	17	45.4	29.4 – 61.5	0.044	0.607
Male	161	28	40.6	30.6 – 50.6		50	16	62.5	41.7 – 83.4		111	12	30.4	20.4 – 40.3		**0.001**
Karyotype																
Intermediate	119	29	51.4	38.5 – 64.4		45	15	58.7	38.7 – 78.6		75	14	44.4	29.4 – 59.4		0.110
Unfavorable	100	13	30.4	18.7 – 42.1	**<0.001**	36	9	52.0	26.7 – 77.3	0.136	64	4	13.3	8.6 – 18.0	**<0.001**	**0.007**
Favorable	24	14	115.0	82.9 – 147.0		9	5	116.0	66.2 – 165.1		15	9	110.2	70.9 – 149.4		0.915
Unknown	23	3	32.9	18.4 – 47.3		8	1	37.7	8.9 – 66.4		15	2	27.6	14.5 – 40.7		0.704
WBC count																
$<100\times10^9$/L	250	52	45.4	36.9 – 53.8	0.344	88	27	61.2	45.0 – 77.4	0.213	162	25	36.8	27.4 – 46.2	0.821	**0.003**
$\geq100\times10^9$/L	30	7	40.6	18.8 – 62.5		13	3	39.6	6.4– 72.8		17	4	21.2	9.4 – 33.1		0.787
AML Presentation																
De novo	201	54	54.7	44.2 – 65.3		76	28	69.0	50.5 – 87.6		125	26	45.7	33.6 – 57.8		**0.028**
Secondary	79	5	21.9	12.7 – 31.2	**<0.001**	25	2	33.1	13.1 – 53.1	**0.021**	54	3	15.0	8.2 – 21.7	**<0.001**	**0.039**

*n=266 for karyotype– not available for 14 patients

Mean Survival and 95% CI were calculated from Kaplan-Meier analyses of Survival time in Months; p values based on Log Rank (Mantel-Cox) test of equality between different factor levels of each covariate. Boldface entries represent p values significant at P <0.05.

Log rank tests for equality of survival distributions for different levels of each covariate after adjustment for smoking status showed statistically significant differences for age, karyotype, and AML presentation (data not shown)

Abbreviations: N, number of individuals; N^C, number of censored individuals in each stratum; mths, months; CI, confidence Interval; p, p-value; WBC, white blood cell count at diagnosis; AML, acute myeloid leukemia;

Number of Events, Censored Individuals: Overall: Events: 222, Censored: 59; Never Smokers: Events: 71, Censored: 30; Ever Smokers: Events: 151, Censored: 29

Table 4

Multivariate analysis for OS by selected characteristics based on Cox Proportional Hazard Modeling (n=266)

Characteristic	N	HR	95% CI	P	Test for Interaction: p value
Smoking Status					
Never	98	1.000	(Referent)		**N/A**
Ever	168	1.637	1.212–2.211	**0.001**	
Gender					
Female	114	1.000	(Referent)		0.431
Male	152	1.052	0.789 – 1.404	0.728	
Age					
<60 years	155	1.000	(Referent)		0.522
≥60 years	111	1.962	1.456 – 2.644	**<0.001**	
AML Presentation					
De novo	198	1.000	(Referent)		0.227
Secondary	68	1.339	0.971 – 1.846	0.075	
WBC count					
$<100\times10^9$/L	236	1.000	(Referent)		0.250
$\geq100\times10^9$/L	30	1.658	1.058 – 2.598	**0.027**	
Karyotype					
Intermediate	119	1.000	(Referent)		
Unfavorable	100	2.049	1.507–2.785	**<0.001**	0.242
Favorable	24	0.475	0.243–0.926	**0.029**	
Unknown	23	1.212	0.743–1.975	0.442	

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; N, number; WBC, white blood cell;

Gender, age, AML presentation, WBC Count, karyotype, and smoking status were entered into the model concurrently to assess hazard ratio. P-value based on Cox Proportional Hazard Modeling after adjusting for all other covariates. Boldface entries represent statistically significant hazard ratios compared to referent group.

Tests for interaction were performed between variable of interest and smoking status (never vs. ever) in separate Cox Proportional Hazard Models, adjusting for all other covariates.