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The impact of smoking on outcomes among patients undergoing hematopoietic stem cell transplant for the treatment of acute leukemia

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Abstract

A paucity of research exists examining the potential impact of tobacco use on cancer treatment outcomes, especially among patients treated with hematopoietic stem cell transplantation (HSCT). A retrospective cohort study design was utilized to examine the impact of smoking on duration of hospitalization and overall survival among 148 consecutive patients undergoing HSCT for treatment of acute leukemia from 1999 to 2005. Of the 148 patients, 15% reported current smoking, 30% former smoking, and 55% never used tobacco. Patients were followed for a median 3.5 years (Interquartile Range= 2.1-5.5). Compared to no history of smoking, current smoking was associated with worse pre-HSCT pulmonary function tests ($p < .02$ in each case), more days hospitalized (46.2 versus 25.7 days, $p = 0.025$, and poorer overall survival (HR=1.88; 95% CI 1.09-3.25). Results were similar after multivariate adjustment, although the association with overall survival attenuated slightly (HR=1.75, 95% CI 1.00-3.06). Current smoking appears to adversely affect the number of days hospitalized post-HSCT and overall survival. Translational research focused on interventions to promote tobacco cessation may lead to improved HSCT outcomes.

Keywords

tobacco; smoking; health behavior; life style; neoplasms; leukemia; transplants; hematopoietic stem cell transplantation

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Introduction

Studies examining the impact of smoking on cancer survivor outcomes have focused on tobacco-related cancers, such as those of the lung, head, and neck. Within these populations, comprehensive reviews observe associations between smoking and: 1) reduced treatment efficacy (chemotherapy, radiotherapy, surgery), 2) delayed surgical healing, 3) creation or exacerbation of common comorbidities, 4) increased risk of some secondary cancers and cancer recurrence, and 5) decreased survival.[1, 2] There are few outcome studies focused on cancer types with etiology not strongly associated with tobacco use, including hematological malignancies. Further research is needed to assess the impact of tobacco use on cancer treatment outcomes among these understudied cancer populations.[2, 3]

According to studies utilizing the population-based National Health Interview Survey, lifetime smoking prevalence is approximately 45-60% among cancer survivors, slightly higher than rates of 37-53% among non-cancer controls. Current tobacco use among cancer survivors ranges from 7.7% to 42.6% and decreases with advancing age. Younger survivors are more likely to continue smoking.[4, 5] Additionally, lower levels of social support and socioeconomic status are generally associated with higher prevalence of tobacco use. [6]

Few studies have examined the impact of smoking on Hematopoietic Stem Cell Transplantation (HSCT) outcomes. Among HSCT recipients, the estimated prevalence of lifetime smoking ranges from 22-62%, and current smoking ranges from 7-17%.[7-14] Observed associations between lifetime smoking history and HSCT outcomes include higher rates of leukemia recurrence,[9] diffuse alveolar damage,[10] infection, Pulmonary Transplant Related Mortality (PTRM), [11] treatment related mortality,[12] and lower rates of disease-free[12] and overall survival.[12, 13] Smoking in the time period after diagnosis and prior to transplant has also been associated with lower overall survival.[15] Null findings have been observed between smoking and mortality,[9, 14] and acute and chronic graft verses host disease.[12] Therefore we evaluated the hypothesis that smoking would be related to worse HSCT outcomes, specifically longer duration of hospitalization and shorter survival time.

Materials and Methods

This retrospective cohort study was reviewed and approved by the Mayo Clinic Institutional Review Board. A total of 153 consecutive adult HSCT recipients were treated for acute leukemia between 1999-2005, in an outpatient-based program. Inclusion criteria for this study were: 1) aged 18 years or older, 2) diagnosis of acute leukemia, 3) treatment with HSCT, 4) patient consent for use of their medical records for research, and 5) completion of the standard hematology pre-HSCT evaluation. One patient was excluded based on an abbreviated hematology evaluation prior to HSCT and 4 patients were excluded based on sole use of smokeless tobacco, thus 148 patients met all eligibility criteria and form the basis of this report.

All study variables (demographic variables, type of leukemia, disease status, transplant type, diagnosis date, transplant date, pulmonary function tests, Body Mass Index (BMI), dates of hospitalization within one year post-HSCT, dates of infections, survival status, cause of

death, and absolute neutrophil count and platelet count as parameters of hematopoietic reconstitution) except smoking status were collected in standardized formats. Smoking was abstracted from three medical record sources (standardized patient registration form, hematology consultation and follow-up notes, and clinical health psychology consultation and follow-up notes) by two trained research assistants who independently coded the patient's smoking status. Incongruent ratings were reviewed and resolved by the primary author without knowledge of patient outcomes. Pre-transplant variables, hospitalization days, and survival status were electronically imported from standardized forms within the medical record, which is maintained in compliance with Foundation for the Accreditation of Cellular Therapy.[16] Patients approved for transplant must meet pre-transplant exclusion criteria, including ejection fraction > 40%, pulmonary forced expiratory volume in one second > 50%, and diffusing capacity of the lung for carbon monoxide > 50%. In the context of this outpatient-based HSCT program, patients are hospitalized if they develop neutropenic fever and one of the following conditions: elevated serum lactate level (> 2.3 mmol/L), pulmonary infiltrates documented by chest radiograph, hypoxia, or hypotension. Most patients experience hospital admission, but spend the majority of their post-transplant recovery in outpatient status. They reside near the hospital in transplant patient housing or hotels, and attend daily or near daily outpatient visits after comprehensive education on infection prevention precautions (e.g., wearing a mask, food hygiene, hand hygiene). Hematopoietic reconstitution outcomes were electronically imported from daily complete blood counts, which are performed until reconstitution cut-offs are met. Reconstitution was defined as platelet count (PLT) >20,000 × 10(6)/L and absolute neutrophil count (ANC) >500 × 10(6)/L for three consecutive days, unsupported by blood product transfusion.

Smoking was categorized into three categories, namely current (smoking <= 1 year prior to HSCT), former (quit > 1year prior to HSCT) or never. All patients had smoking status documented in their medical record. The year prior to HSCT was chosen to characterize current use based on high relapse rates within 1 year following a reported cessation attempt in both the general population and following cancer treatment (33-90%). [2], [6] This timeframe also minimizes self-reporting bias in which patients are less likely to reveal active smoking in the context of cancer treatment.[17], [18]

Data Analysis

Demographic variables were compared among the three groups using analysis of variance and chi-square tests as appropriate. Analyses were performed to determine if smoking was associated with number of hospitalization days within 1 year post-HSCT and overall survival. Survival status was assessed via annual letters to patients and queries of institutional databases. Secondary analyses also examined the impact of smoking on potential mediators, including the number of infections within 1 year post-HSCT (documented bacterial, fungal and viral infections and suspected but not microbiologically proven fungal infections), and time to hematopoietic reconstitution (ANC and platelet counts). For these analyses subjects who did not achieve hematopoietic reconstitution were censored at the date of their last follow-up. Both univariable and multivariable regression analyses were performed. Number of hospitalization days and number of infections were assessed using linear regression while overall survival and time to hematopoietic

reconstitution parameters were assessed using proportional hazards regression. For the multivariable analyses, transplant type (allogeneic versus autologous), disease status [first or second Complete Remission (CR1 and CR2) versus Primary Induction Failure (PIF) versus other], and age were included as covariates. In all cases, two-sided p-values <0.05 were considered statistically significant.

Results

Study participants (N=148) underwent HSCT a mean of 1.3 years after diagnosis of acute leukemia and were followed for a median of 3.5 years (Interquartile Range= 2.1- 5.5). Primary diagnoses were Acute Myelogenous Leukemia (AML, n= 118) and Acute Lymphoblastic Leukemia (ALL, n= 30). Most patients were in first (CR1) or second complete remission (CR2) and received an allogeneic graft (74%, see Table 1). The majority (71.6%) received a conditioning regimen of Cytoxan plus total body irradiation (n= 106), with 11 other conditioning regimens represented. Smoking within the year prior to HSCT was reported by 14.9% (current use, n= 22) of participants, while 30.4% (n= 45) reported use prior to 1 year pre-transplant (former use), and 54.7% (n= 81) denied any history of smoking. In terms of hematopoietic reconstitution, 132 (89.2%) achieved ANC >500 × 10(6)/L and 107 (72.3%) achieved PLT >20,000 × 10(6)/L. Patients experienced a median of 0 (Interquartile Range= 0-3) infections in the first year post-HSCT.

Table 1 summarizes demographic and clinical variables by smoking categories. Mean patient age was 44 ± 15 years with a range of 18-72 years. Patients were predominantly Caucasian (97%), married (70%), and male (54%). On average, patients who used tobacco in the year prior to HSCT were younger (42.1± 12.8) than patients who had discontinued use (52.0± 13.1). They were also less likely to be married. Patients who discontinued use were more likely to have an autologous transplant.

Hospitalization Days

Patients were hospitalized a mean of 30 ± 32 days with a mean of 2 hospital admissions in the year following HSCT. Table 2 summarizes non-hematopoietic HSCT outcome variables by smoking status. Current smokers had a mean (± S.D.) of 46 ± 46 hospitalization days in the year following HSCT, compared to means of 30 ± 31 and 26 ± 25 hospitalization days associated with former and never smoking, respectively (p=0.025). After adjusting for transplant type, disease status, and age, smoking was significantly associated with number of days hospitalized (p=0.009). There was a trend for the multivariate adjusted relationship between current smoking and number of hospital admissions (p= .062).

Survival

There were 101 participants who died by study end. Table 3 summarizes the median, 1-, 2-, and 3- year overall survival rates by smoking status. Compared to never smokers, previous smoking (hazard ratio (HR) =1.31; 95% CI: 0.85-2.04) and current smoking (HR=1.88; 95% CI: 1.09-3.25) had poorer overall survival, and the trend test was marginally significant (p=0.07). These results marginally attenuated after multivariate adjustment (previous

smoking, HR =1.17; 95% CI: 0.72-1.91; current smoking, HR =1.75; 95% CI: 1.00-3.06) as did the trend test (p= 0.14). Table 4 summarizes cause of death by smoking status.

Pulmonary/respiratory cause of death was higher in previous and current smokers (6% of never smokers, 20% of previous smokers, and 26% of current smokers). As expected, comparison of pre-transplant pulmonary function tests revealed worse function for current smokers (Table 1). The percent of predicted forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide adjusted for hemoglobin (DLCO), as well as forced expiratory flow at 25% to 75% capacity (FEF 25-75) were all lower in current verses never smokers. Other potential mediators of survival and hospitalization (i.e., time to hematopoietic reconstitution and number of infections) were not associated with smoking (Table 2, Table 5).

Discussion

The rate of current smoking within this sample was in the range reported in prior studies of HSCT candidates and survivors. Compared to patients with no history of smoking, current smoking was related to an average of 21 more days of hospitalization in an outpatient-based HSCT program in the first year post-HSCT. This translates to average hospitalization charges that are $126,434 higher per patient in the first year post-HSCT, based on national average charges for hospitalization with leukemia as primary diagnosis.[19] Current smoking was associated with worse pre-transplant pulmonary function tests, which may have contributed to increased hospitalization days. These finding suggests that current smoking is a risk factor for poorer health status and may impair recovery from HSCT. Demographic factors associated with former smoking status among HSCT patients were similar to those found to predict tobacco cessation in the general population, including higher levels of social support (married) and older age. [6]

Overall the current study supports the available literature documenting the negative impact of tobacco on HSCT outcomes. Marks and colleagues published the first study to observe a dose-response effect of lifetime smoking on mortality in a sample of 2818 patients treated for CML.[12] Specifically they found a difference in treatment related mortality rates of 22% higher for “high dose” smokers (defined as a lifetime history of greater than both one pack per day and 10 pack-years) verses never smokers 5 years post-HSCT. Marks and colleagues also observed an 18% higher mortality rate and 25% lower disease free survival. Importantly, the Marks et al. observations persisted while controlling for a prognostic risk score. In our study, compared to never smokers, current smokers had 18%, 27%, and 24% lower survival rates, respectively at 1-, 2-, and 3-years post-HSCT, consistent with Marks et al. However, this difference did not reach statistical significance possibly related to a smaller sample size. Hoodin and colleagues observed a link between smoking until diagnosis and mortality.[15]

Other HSCT studies have linked smoking to pulmonary complications and infection. Among a sample of predominantly leukemia survivors treated with allogeneic HSCT, smoking within 2 months prior to transplant was an independent risk factor for PTRM.[11] In this group of 146 consecutive HSCT patients, 38% of smokers (defined as smoking within 2 months

prior to transplant and having a 2 year history of smoking) and 5% of non-users developed Pulmonary Transplant Related Mortality. An autopsy study observed that smoking history was a predictor of diffuse alveolar damage among HSCT recipients, affecting 64% of patients with a smoking history versus 37% of patients without a smoking history. Notably, this study observed that 89% of deceased HSCT recipients had a pulmonary complication at autopsy, the majority of which were undiagnosed prior to death. [10] In our sample, death attributed to pulmonary toxicity or respiratory distress was documented for 6% of never smokers, 20% of previous users, and 26% of current users. Pre-HSCT pulmonary function was significantly worse for smokers in our study, and is thus a likely contributing factor to pulmonary damage and mortality in the above studies. A study of 367 consecutive multiple myeloma survivors treated with autologous HSCT revealed pre-transplant smoking as an independent risk factor for infection, with 37% of current smokers versus 27% of former/never smokers developing a post-HSCT infection.[13] In our sample, death attributed to infection was documented for only 9 participants (11% of never smokers, 8% of previous smokers, and 5% of current smokers).

Short-term studies are rare and do not support a link between smoking and early HSCT complications. A retrospective chart review of 339 consecutive HSCT recipients (mixed disease) revealed an 8-9% increased risk for severe pulmonary complications within 60 days post-transplant among patients with a history of cigarette smoking, [7] but it did not reach statistical significance. A study of sinusitis in 100 HSCT patients undergoing allogeneic transplant did not find a significant difference in frequency of dichotomous sinusitis variables (clinical disease severity, CT scan opacity) associated with history of smoking.[8] Given the paucity of short-term outcome studies, further research is warranted.

Strengths of the current study include a consecutive patient sample with complete data on smoking, baseline pulmonary function tests, and the novel study context of an outpatient-based program that allowed for examination of hospitalization as a study outcome. To our knowledge, ours is the first study to examine duration of cessation in relation to HSCT outcomes. It is also the first to document a significant relationship between smoking and duration of hospitalization. Another strength of our study is use of a standardized coding system and multiple raters to minimize bias related to patient-report and health care provider-report methodologies, yielding smoking prevalence estimates congruent with large general population-based studies that are expected to approximately match true HSCT smoking prevalence rates. Limitations of this study include reliance on patient-reported smoking status (as all other cited studies) and medical records as source documentation (as all other studies besides one).[9] Medical records were not available for hospitalizations outside our transplant center, thus hospitalizations outside our transplant center were not included in study analyses. However, there was not a significant association between in-state residence and smoking status. Detailed information regarding reasons for hospitalization, post-transplant complications, types of infection, cytogenetic risk, graft verses host disease, and prognostic scores were not recorded in a standard manner amenable to data abstraction. Tobacco quantity and frequency information was not generally recorded in the medical record, and thus dose-response relationships between tobacco and HSCT outcomes were not testable.

The scientific literature documenting a link between tobacco and adverse medical outcomes presents possible mediating mechanisms to explain the effects of tobacco on HSCT outcomes. Smoking is associated with reduced immune functioning (e.g., natural killer [NK] cell activity), increased pro-inflammatory cytokines that may predispose patients to both respiratory and systemic infections, [20] and comorbidity. [21] This suggests even greater risk for patient groups such as HSCT that experience compromised immunity.

Theoretically, tobacco cessation might improve HSCT outcomes, as has been demonstrated in tobacco-related cancer populations (e.g., survival[22]) and is suggested by the significant association of current smoking to hospitalization in our study. Accounting for smoking in program statistics may improve estimates of risk for individual patients. Finally, if replicated and disseminated, the effect of tobacco on HSCT outcomes may motivate more patients and their providers to pursue appropriate tobacco cessation interventions, increasing tobacco abstinence rates. An association between duration of smoking cessation and outcomes may also motivate cessation as early as possible in patient care.

To our knowledge, ours is the first study observing an association between smoking and longer duration of hospitalization in HSCT patients. This is also the first study to associate current smoking with adverse HSCT outcomes. A need exists for prospective cohort studies examining the impact of smoking on HSCT outcomes. Future studies would be improved by standardized assessment and documentation of smoking status, a practice that is congruent with suggested practice guidelines.[6] In particular, lifetime quantity of smoking (pack-years) and duration of cessation would allow examination of potential dose-response relationships between tobacco amount, cessation time, and HSCT outcomes. Future research should include a broader range of patient outcomes, including quality of life, return to work, health care related costs, and fatigue. Additionally, assessment of potential mediators such as NK-cell activity, pro-inflammatory cytokine levels, and standardized comorbidity scores might reveal mechanisms underlying relationships between smoking and HSCT outcomes. Lastly, barriers to tobacco cessation, including patient cognitive beliefs,[2] motivational readiness, social support, and secondhand smoke exposure[6] should be assessed to promote development of interventions that are viewed by patients as relevant and integrated into their clinical care.

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TABLE 1

Demographic and Clinical Characteristics Among HSCT Recipients (N=148)*

Variable	Overall (N=148)		Never (N=81)		Previous (N=45)		Current (N=22)		P-value*
Female Gender	68	(46%)	42	(52%)	18	(40%)	8	(36%)	0.16
Age	44.3	± 14.7	40.7	± 14.5	52.0	± 13.1	42.1	± 12.8	<0.001
Race									0.65
Black	2	(1%)	1	(1%)	1	(2%)	0	(0%)	
Hispanic	4	(3%)	3	(4%)	0	(0%)	1	(5%)	
Caucasian	136	(97%)	74	(95%)	44	(98%)	18	(95%)	
Married	95	(70%)	50	(69%)	39	(89%)	6	(30%)	<0.001
Disease status at treatment									0.25
CR 1	52	(35%)	23	(28%)	18	(40%)	11	(50%)	
CR 2+	39	(26%)	25	(31%)	12	(27%)	2	(9%)	
Other	41	(28%)	23	(28%)	11	(24%)	7	(32%)	
PIF	16	(11%)	10	(12%)	4	(9%)	2	(9%)	
Type of transplant									<0.001
Allogeneic	110	(74%)	68	(84%)	24	(53%)	18	(82%)	
Autologous	38	(26%)	13	(16%)	21	(47%)	4	(18%)	
Time from diagnosis to HSCT (years)	1.3	± 1.8	1.1	± 1.1	1.4	± 1.8	1.5	± 3.1	0.48
FEV1 PP	91.4	± 15.5	94.6	± 14.3	88.7	± 17.8	85.5	± 12.2	0.019
FEF 25-75	3.0	± 1.1	3.4	± 1.1	2.5	± 0.8	2.8	± 1.1	<0.001
DLCO PP	74.3	± 15.3	74.9	± 14.2	77.8	± 14.9	64.9	± 16.8	0.004
BMI	27.3	± 5.2	27.0	± 4.3	28.7	± 6.1	24.0	± 3.3	0.12

*All variables are reported as n (%) or mean ± standard deviation (SD). Chi-square test or analysis of variance (ANOVA) as appropriate. CR 1= first complete remission, CR 2+= second or greater complete remission, PIF= primary induction failure, PP= percent predicted, FEV1= forced expiratory volume in one second, FEF 25-75= forced expiratory flow at 25% to 75% capacity, DLCO= diffusing capacity of the lung for carbon monoxide adjusted for hemoglobin.

TABLE 2

Hospitalization and Infection Outcomes Among HSCT Recipients (N= 148)*

Variable	Overall (N=148)		Never (N=81)		Previous (N=45)		Current (N=22)		P-value	Adjusted P-value
Days hospitalized	30.0	± 31.6	25.7	± 25.3	29.8	± 31.4	46.2	± 46.3	0.025	0.009
Number of hospital admissions	2.4	± 2.0	2.2	± 1.9	2.5	± 1.8	3.0	± 2.8	0.19	0.062
Number of infections	1.9	± 2.9	1.9	± 3.0	1.8	± 2.6	2.2	± 3.2	0.86	0.86

*Linear and multivariable-adjusted regression (age, disease status, transplant type) from the time of HSCT to 1 year post-HSCT. Hospital admissions and days hospitalized are not planned in the context of an outpatient-based program. Reported as mean ± standard deviation.

TABLE 3

Median Survival by Tobacco use Status Among HSCT Recipients (N= 148)

Tobacco use status	Median Survival Time (years)	Survival (95% CI) at 1 year	Survival (95% CI) at 2 years	Survival (95% CI) at 3 years
Never (N= 81)	1.16	51.7%(41.6,64.2)	46.1%(36.1,58.9)	42.9%(33.0,55.9)
Previous (N= 45)	0.80	42.2%(30.0,59.4)	30.6%(19.6,47.7)	25.7%(15.5,42.6)
Current (N= 22)	0.44	33.5%(18.3,61.2)	19.1%(7.9,46.2)	19.1%(7.9,46.2)

TABLE 4

Cause of Death by Tobacco Use Status Among Deceased HSCT Recipients (N=101)

Cause of Death	**Never (N=46)**		**Previous (N=36)**		**Current (N=19)**	
	N	%	N	%	N	%
Relapsed/Progressive Disease	26	(57%)	19	(53%)	9	(47%)
Non-relapse Mortality						
Respiratory	3	(7%)	7	(19%)	5	(26%)
Other Organ Toxicity	11	(24%)	4	(11%)	3	(16%)
Acute Graft Versus Host Disease	1	(2%)	0	(0%)	1	(5%)
Infections*	5	(11%)	3	(8%)	1	(5%)
Neurological**	0	(0%)	1	(3%)	0	(0%)
Secondary Malignancy	0	(0%)	1	(3%)	0	(0%)
Graft Rejection or Failure***	0	(0%)	1	(3%)	0	(0%)

* Infection is recorded as cause of death only in the context of positive culture.

** Neurological cause of death is recorded in the context of acute neurological event (e.g., intracranial bleed).

*** Rejection is defined as loss of all donor chimerism. If concurrent with relapse, relapse is recorded as cause of death.

TABLE 5

Hematopoietic Reconstitution Outcomes by Tobacco Status Among HSCT Recipients (N= 148)*

Reconstitution parameter	Overall (N=148)		Never (N=81)		Previous (N=45)		Current (N=22)		P-value	Adjusted P-value
ANC >500	17		17		15		17		0.32	0.44
PLT >20,000	25		24		27		18		0.57	0.59

* Median time (days) to given endpoints are presented with p-values from unadjusted and multivariable-adjusted (age, disease status, transplant type) proportional hazards regression. ANC= Absolute Neutrophil Count × 10(6)/L. PLT= Platelet count × 10(6)/L.