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Age and number of apheresis days may predict for development of Secondary Myelodysplastic Syndrome and Acute Myelogenous Leukemia after transplantation for lymphomas

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Abstract

BACKGROUND: The goal of our study was to find predictors for the development of secondary myelodysplastic syndrome or acute myelogenous leukemia (s-MDS/AML) in patients with relapsed or refractory lymphoma who received high-dose chemotherapy and autologous stem cell transplantation (ASCT).

STUDY DESIGN AND METHODS: We conducted a retrospective review of 295 patients with relapsed or refractory lymphoma who had undergone their first stem cell collection and ASCT. Patient, disease, and treatment characteristics were collected. The primary goal of this study was to analyze the association between the number of apheresis days needed to collect the requisite stem cell dose in addition to the previously described factors such as age, sex, number and type of prior chemotherapeutic regimens, disease type and status, and the risk of developing s-MDS/AML.

RESULTS: Twenty-two patients of 295 were diagnosed with s-MDS/AML after a median follow-up of 62 months. Multivariate analysis using a classification and regression tree showed that the incidence of s-MDS/AML was lowest in patients who were not more than 55 years old at transplantation and in whom the target cell dose was collected in fewer than two apheresis sessions (5-year cumulative incidence, 1%), whereas incidence was highest in patients who were more than 55 years old at transplantation and who received a transplant more than 21 months after their initial lymphoma diagnosis (5-year cumulative incidence, 20%).

CONCLUSION: Our study defines a subset of relapsed or refractory lymphoma patients who should be closely monitored for development of s-MDS/AML after high- dose chemotherapy and ASCT.

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Keywords

Apheresis days; Autologous stem cell transplantation (ASCT); secondary myelodysplastic syndrome (s-MDS) / acute myeloid leukemia (AML); lymphoma

BACKGROUND

Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (NHL) are commonly treated with combination of chemotherapy and radiotherapy[1,2]. Both chemotherapy and radiotherapy can increase the risk of subsequent clonal hematologic neoplasms, such as treatment-related secondary myelodysplastic syndrome (s-MDS) or acute myeloid leukemia (AML)[3]. High-dose chemotherapy and autologous stem cell transplantation (ASCT) is an effective consolidation therapy for patients with HL and NHL, in particular when the disease has relapsed, is refractory or has high risk features[4,5]. Several retrospective studies have shown that the risk of secondary malignancies (AML, s-MDS) after ASCT is increased significantly compared to the general population[6–8]. The cumulative probability of developing s-MDS or AML after ASCT for HL and NHL ranges between around 4 to 18% at 5 years[9–11]. Some of the risk factors that may predict for developing s-MDS or AML after ASCT are the number of chemotherapy cycles received pre transplant[12], agent type of pre-ASCT chemotherapy[13], pre-ASCT radiation therapy[14], patient age at transplantation[15], peripheral blood counts at the start of mobilization[16], and use of peripheral blood as source of stem cells[17]. More than 5 days needed to collect peripheral-blood hematopoietic stem-cells before ASCT has also been suggested to be an independent predictor for development of s-MDS or AML after ASCT[15]. In this study, we analyzed the association between the number of apheresis days needed to reach the target stem cell dose in addition to the previously described factors such as age, gender, number and type of prior chemotherapeutic regimens, disease type and status and the risk of developing s-MDS / AML. Secondary objectives of the study were to determine factors that may predict the stem cell yield on the first day of apheresis.

MATERILAS AND METHODS

A total of 295 consecutive patients who underwent their first apheresis and ASCT at The University of Texas MD Anderson Cancer Center between January 2008 and July 2011 for HL or NHL were recruited in this study. This retrospective study was approved by the Institutional Review Board. The data was collected from the Departmental Database and patient's medical records. Patient demographics, disease, and treatment characteristics were recorded

Peripheral blood stem cells were collected after the penultimate round of chemotherapy followed by filgrastim 10 mcg/kg/day (G-CSF). Leukapheresis was started when the circulating peripheral blood CD 34+ count was > 10μL. A total of 3 x the total blood volume was processed using the COBE Spectra. Stem cells were quantified using the ISHAGE protocol[18]. The target cell dose was 5×10^6 $CD34^+$ cells/kg, with a minimum acceptable dose of 2×10^6 $CD34^+$ cells/kg.

After ASCT patients were followed every 3 months for the first year and then every 6 months for 5 years or as clinically indicated. The diagnosis of s-MDS or AML was made in accordance with the French-American-British (FAB) classification based on cytomorphologic findings of bone marrow biopsies.[19,20]

STATISTICAL CONSIDERATIONS:

The primary objective of the study was to assess the incidence and predictors of s-MDS/AML. The cumulative incidence (CI) of s-MDS/AML was estimated considering death prior to the development of secondary malignancy as a competing event. Cox proportional-hazards regression analysis was used to assess the predictors of s-MDS/AML on univariate analysis. Classification And Regression Tree (CART) analysis was used to assess predictors of s-MDS/AML in multivariate analysis in order to account for potential interaction effects. Predictors of s-MDS/AML evaluated on univariate analysis included: gender, age at transplant, age at diagnosis, histological type, disease status at transplant (complete remission, partial remission, stable or progressive disease) number of cycles of chemotherapeutic regimens prior to transplant (≤3 and >3), prior fludarabine therapy, prior radiation therapy, time from diagnosis to transplant (months), CD34+ cell dose/kg collected on first day of apheresis, and number of apheresis days. Factors that were significant on univariate analysis were considered in multivariate analysis. Actuarial overall and progression free survival were estimated by the Kaplan-Meier method. The cumulative incidence method accounting for competing risks was used to estimate the incidence of non-relapse mortality (NRM) and of progression of the underlying primary malignancy. All statistical tests were two-sided and P values ≤0.05 were considered to be statistically significant. Statistical analysis was performed using STATA 11. (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP).

RERULTS

A total of 295 patients underwent stem cell mobilization and ASCT during the study period. Pre-transplant characteristics are summarized in Table 1. The median number of days to reach the target CD34+ cell dose was 2 (range 1–10) days. The median CD34+ cell dose collected was 2.95×10^6/kg (range, 0.2–101). All patients engrafted. Median time to neutrophil engraftment after transplant was 10 days (range, 7–16). Median time to reach platelet count > 20,000 $\times 10^9$/L was 11 days (range, 7–114). Ten patients did not engraft platelets and 7 of whom died (data not available for 3 patients). After a median follow up time of 62 (5–88) months in survivors actuarial overall survival at 5 years was 66% (95% CI 60–71); progression-free survival was 51% (95% CI 45–57); non-relapse mortality was 6% (95% CI 4–9); and incidence of disease progression was 28% (95% CI 23–34).

Secondary MDS/AML

A total of twenty-two subjects were diagnosed with s-MDS or AML after a median follow-up in survivors of 62 (range 5–88) months. Twenty-one of the 22 cases were diagnosed within 5 years of transplant. The cumulative incidence of s-MDS/AML at 5 years was 8% (95% CI 5–12). Two patients had non clonal abnormalities of chromosome 7 pre transplant and one patient had del 20q in 2 metaphases by conventional cytogenetic analysis. The most

common chromosomal alteration after diagnosis of MDS/AML was complex cytogenetics, or alterations of chromosome 7 or 5 in 12 patients (50%). At last follow up 19 of the 22 patients had died at a median of 6 months since the diagnosis of the secondary malignancy. The results of univariate analysis of risk factors for development of sMDS/AML within 5 years of ASCT are summarized in Table 2.Three are alive after undergoing allogeneic stem cell transplantation. Secondary MDS/AML was the most common cause of non-relapse mortality.

On univariate analysis, age > 55 years at diagnosis or at transplant, days to collections of target stem cell dose (> 2 days), and time from diagnosis to transplant (> median: 21 months) predicted for the development of s-MDS / AML within 5 years of transplant. Results of the multivariate analysis using CART (classification and regression tree) revealed 4 subgroups of patients with increasing risk of developing s-MDS / AML within 5 years of transplant. The incidence of s-MDS / AML was lowest in patients who were ≤ 55 years old at transplant and were able to collect the target cell dose in < 2 apheresis sessions (n=102, 5 years CI 1%) and highest in patients who were older than 55 years of age at transplant and were transplanted > 21 months after their initial lymphoma diagnosis (N=67, 5 years CI 20%), (Figure 1).

DISCUSSION

Several studies have evaluated factors that may predict for development of s-MDS / AML post ASCT in patients with refractory / relapsed HL and NHL. In the present analysis we were able to identify 2 major predictors for development of sAML/MDS in patients undergoing ASCT for lymphoma, Patients who were older than 55 years of age at transplant had the highest risk. By further risk stratification using CART we were able to detect different predictors of secondary malignancy in younger versus older patients.. In patients who were 55 years of age or younger, the number of days needed to collect the target cell dose impacted the risk of developing s-MDS/AML. Younger patients who collected the target dose in 2 days of apheresis or less had a significantly lower risk of developing s-MDS/AML versus those who needed more than 2 days to collect the target dose. On the other hand, in patients who were older than 55 years of age the, longer duration between diagnosis and transplantation (> 21 months) was associated with significantly higher rate of s-MDS / AML. These findings suggest that depending on age, difficult stem-cell harvesting or time from diagnosis to transplant might be a powerful predictor for the development of s-MDS / AML. Notably, the number of days of apheresis needed to collect targeted cell dose was not correlated with the duration from diagnosis to transplant. Association between difficulty of stem cell harvesting and increased incidence of s-MDS / AML after autologous stem cell transplantation for HL and NHL was noted by Kalaycio et al as well[15] and Waterman et. al.[19]. By multivariable analysis, Kalaycio et al. identified tseveral factors as high risk of development of s-MDS / AML: prior exposure to radiation therapy, four or more chemotherapy regimens and more than 5 days of apheresis needed to harvest enough stem cells. Barlogie et al.[20] similarly reported that development of MDS related cytogenetic abnormalities in patients with multiple myeloma treated with intensive chemotherapy was linked to lower CD34 yield at collection, longer time interval from diagnosis to high dose therapy, older age, and lower platelet recovery after transplant. Persistent cytogenetic

abnormalities were also predicted by CD34 yield of less than 3×10^6/kg and need for more than 2 apheresis procedures. Increased number of apheresis itself is not the cause of s-MDS / AML, however, it could be used as a surrogate to identify patients who may be at risk for developing s-MDS / AML after ASCT. It has been suggested that some patients who develop s-MDS/AML post ASCT may already have changes compatible with myelodysplasia pre-transplant. In our study 3 of 22 patients had pre-existing abnormalities of which 2 had non clonal changes. These patients should be followed closely for the onset of s-MDS / AML. In selected cases an allogeneic transplant rather than an autologous transplant may be more appropriate. The outcomes of t-MDS and AML have been poor[21] and survival has been rare..

In summary, our data shows that age, and number of apheresis days to reach target stem cell dose may predict for development of incidence of s-MDS / AML after ASCT for lymphoma in patients 55 years of age or younger. Although the majority of these patients will still benefit from ASCT, those patients identified with these risk factors should be considered for close follow-up for development of s-MDS / AML. In selected patients an allogeneic transplant may be more appropriate.

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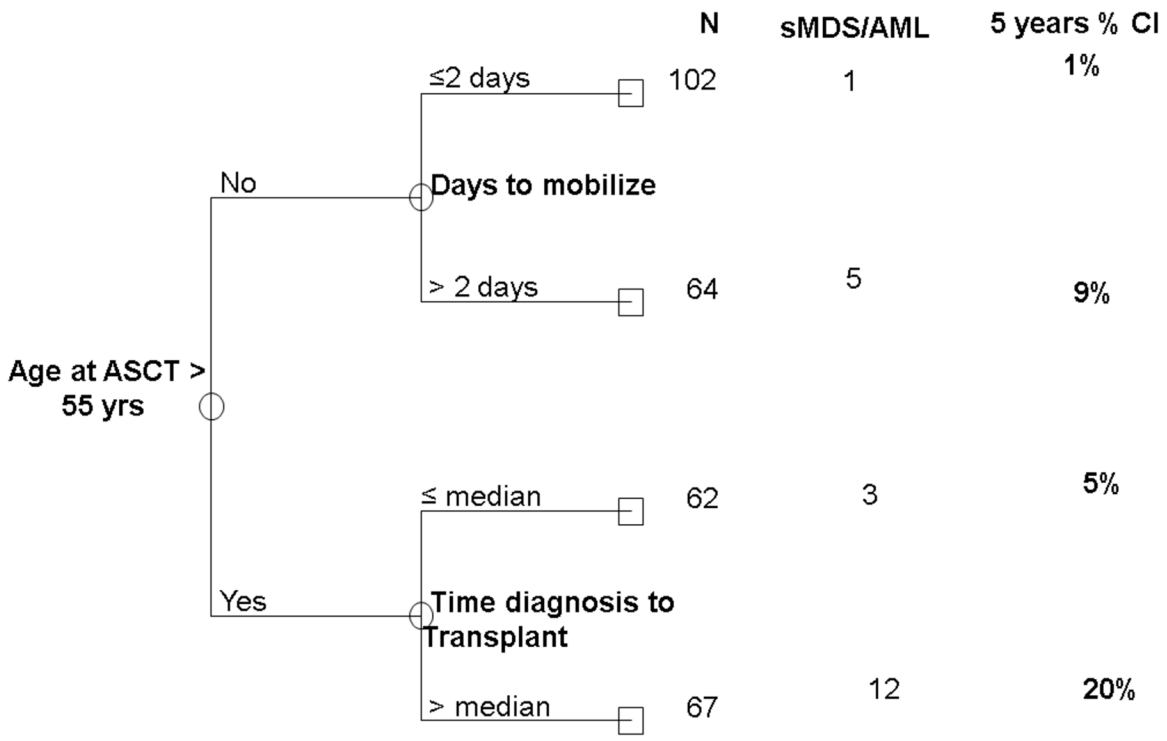

Figure 1.

Classification and regression tree (CART) Analysis for development of s-MDS/AML Abbreviations: ASCT, autologous stem cell transplantation; sMDS/AML, secondary myelodysplastic syndrome/acute myelogenous leukemia; N, number, CI, cumulative incidence;

Table 1.

Pre-Transplant Patient Characteristics

Characteristics	Number (%) N=295
Median Age in years (range)	52 (10–77)
Gender	
Male	181 (61.3)
Female	114 (38.6)
Histology	
-Hodgkin's Lymphoma(HL)	85 (28.8)
-Diffuse Large cell lymphoma(DLBCL)	93 (31.5)
-Follicular lymphoma(FL)	33 (11.8)
-Mantle cell lymphoma(MCL)	15 (5.0)
-Peripheral T-Cell lymphoma (PTCL)	10 (3.3)
-Others	42 (14.2)
Disease status prior to Transplant	
-Complete remission	168 (56.9)
-Partial remission	98 (33.2)
-Stable/progressive disease	29 (9.8)
No. of Prior Chemotherapy regimens	
≤3	241 (81.6)
>3	54 (18.3)
Time from Diagnosis to Transplant (months)	
-Median (range)	21 months (4–333)
Conditioning Regimen for ASCT	
BEAM+/− Rituximab	256 (86.7)
Busulfan/Melphalan +/− gemcitabine +/− rituximab	38 (12.8)
Melphalan+ rituximab	1 (< 1)
Median Stem cells infused/Kg (range)	5.12×10^6 (1.8–24.94)

BEAM: carmustine, etoposide, cytarabine, melphalan

Others: Composite/Discordant histology 18; Hepatosplenic gamma delta non-Hodgkin's lymphoma 3; anaplastic large cell lymphoma (T or B) 9; Burkitt's 4; Angioimmunoblastic T cell non-Hodgkin's lymphoma 7; Mycosis fungoides 2; NK/T cell lymphoma 3; Marginal zone nodal and splenic non-Hodgkin's lymphoma 2.

Table 2:

Univariate analysis of predictors of s MDS /AML

Characteristic	Total	sMDS/AML		
	N=295	Hazards Ratio (HR)	95% CI	P value
Diagnosis				
Non-Hodgkin's Lymphoma	**210**			
Hodgkin's disease	**85**	0.6	0.2–1.8	0.4
Number of apheresis days (median, range)	2 (1–10)			
>2	**139**	2.4	1.0–5.9	0.05
Age at diagnosis, years (median, range)	50 (9–76)			0.003
>55 years	**129**	4.3	1.6–11	
Age at transplant, years (median, range)	52 (10–77)			
Age > 55years	**129**	3.3	1.3–8.6	0.01
CD34 dose collected day 1 (median, range)		2.95 (0.2–101)		
Number of prior chemotherapy cycles				
>3	**54**	1.9	0.7–4.8	0.2
Diagnosis to Transplant				
> median (21 months)	**147**	4.5	1.5–13	0.01
Disease status at transplant				
Not in Complete remission	**77**	**0.9**	0.3–2.4	0.8
Sex				
Female	**114**	0.8	0.3–1.9	0.6
Male	**181**			
Radiation				
Pre transplant	**9**	**3.6**	0.8–16	0.9
Post-transplant consolidation	**14**			
Prior Fludarabine				
Yes	**23**	2	0.6–6.8	0.3