4-1-2012

Autologous Stem Cell Transplant is Feasible in Very Elderly Patients with Lymphoma and Limited Comorbidity

Rebecca L. Elstrom
Weill Cornell Medical College

Peter Martin
Weill Cornell Medical College

Sandra M. Hurtado Rua
Cleveland State University, s.hurtadorua@csuohio.edu

Tsiporah B. Shore
Weill Cornell Medical College

Richard R. Furman
Weill Cornell Medical College

Publisher's Statement

This is the accepted version of the following article: Elstrom, Rebecca L. et al. "Autologous Stem Cell Transplant Is Feasible in Very Elderly Patients with Lymphoma and Limited Comorbidity," American Journal of Hematology, vol. 87, no. 4, 2017, pp. 433-435, doi:10.1002/ajh.23108., which has been published in final form at http://onlinelibrary.wiley.com/doi/10.1002/ajh.23108/full

Authors
Rebecca L. Elstrom, Peter Martin, Sandra M. Hurtado Rua, Tsiporah B. Shore, Richard R. Furman, Jia Ruan, Roger N. Pearse, Morton Coleman, Tomer Mark, John P. Leonard, and Usama Gergis

Autologous stem cell transplant is feasible in very elderly patients with lymphoma and limited comorbidity

Rebecca L. Elstrom, Peter Martin, Sandra Hurtado Rua, Tsiporah B. Shore, Richard R. Furman, Jia Ruan, Roger N. Pearse, Morton Coleman, Tomer Mark, John P. Leonard, and Usama Gergis

In patients with recurrent Hodgkin or non-Hodgkin's lymphoma, autologous stem cell transplantation (ASCT) can offer potential for cure or long-term remission. Because of potential toxicity, elderly patients are usually not considered candidates, but data regarding tolerability and efficacy in this group are lacking. The transplant database at Weill Cornell Medical College was reviewed to identify patients with lymphoma undergoing ASCT at age 69 or greater. Clinical data and comorbidities were correlated with outcome. Twenty-one patients were identified. Sixteen of 19 evaluable patients (76%) achieved complete remission following ASCT, while 2 patients died before response assessment. Median progression-free survival following ASCT was 8 months and median overall survival was 18 months. Age was not predictive of overall survival, but patients 75 and older had inferior progression-free survival compared to younger patients. High-risk status by hematopoietic stem cell transplant comorbidity index (HCT-CI) was associated with short overall survival and high transplant-related mortality. ASCT is feasible and of potential benefit in selected elderly lymphoma patients. Consideration of comorbidities, rather than age alone, may allow selection of patients likely to tolerate and benefit from ASCT.

Non Hodgkin's lymphoma increases in incidence with advanced age. High dose chemotherapy with autologous stem cell transplantation (ASCT) plays an important therapeutic role, particularly in patients with chemosensitive relapses of curable histologies such as diffuse large B cell (DLBCL) and Hodgkin lymphoma (HL), but many patients have not been considered eligible for this approach due to advanced age. The question of whether age alone should be an exclusionary factor for ASCT is controversial.

Recent single center retrospective studies reported conflicting results on the impact of age on transplant outcomes. While limited data demonstrating its feasibility in patients >60 years of age are available, most of the patients included in these studies are between the ages of 60 and 70. Although some reports have suggested higher than expected nonrelapse mortality (NRM) in patients over 60 years of age [1], this finding is not consistent [2 5].

Comorbidity refers to a medical condition existing simultaneously with but independently of a primary disorder. The Charlson comorbidity index [6] (CCI) was developed as a tool to predict mortality in hospitalized patients, assigning a weight to a variety of disorders such as diabetes mellitus, liver dysfunction or pulmonary disease, together defining a score which is predictive of mortality. The hematopoietic stem cell transplant comorbidity index (HCT CI) [7] represents a modification of the CCI to better represent comorbidities identified in the allogeneic stem cell transplant population. Major differences between these indices include incorporation of objective data for measurement of pulmonary, renal, and hepatic dysfunction, in addition to symptoms, and consideration of any prior malignancy as a risk factor, not just malignancies initially treated within 5 years of transplantation. The presence of significant comorbidities, as measured by the CCI or HCT CI, predisposes to increased toxicity in patients over 60, but this factor has been inconsistently associated with mortality.

Many patients in the eighth decade of life or beyond have excellent performance status and prelymphoma overall health. At our center, age has not been routinely used as an exclusion criterion for this treatment modality. We therefore examined outcomes of patients who were 69 and older at the time of transplantation to determine whether ASCT is feasible in this population, and whether comorbidities are predictive of NRM and overall survival (OS).

Twenty one patients aged 69 or greater (range 69 86, median 71) were identified who had undergone autologous stem cell transplant for lymphoma and had records available for review; characteristics are shown in Table I. Five patients were 75 years of age or older, and 2 patients were over the age of 80 (83 and 86 years old).

All patients underwent cytotoxic conditioning regimens and subsequently received autologous stem cells. Conditioning regimens for most patients consisted of BCNU, cyclophosphamide, and etoposide (BCV), BCNU, etoposide, cytarabine, and melphalan (BEAM), or similar regimens. Two patients were treated with cyclophosphamide and total body irradiation (TBI), and one received mitoxantrone, thiotepa, and cyclophosphamide.

Neutrophil engraftment occurred in 19 patients, while 2 patients died before engraftment could be evaluated. Platelet engraftment occurred in 16 patients, while 3 remained platelet transfusion dependent. Median time to neutrophil engraftment was 11 days (range 9 26 days), and median time to platelet engraftment was 21 days (range 13 51 days).

Sixteen patients (76%) achieved a complete remission (CR) following ASCT, while three patients did not achieve CR. Two patients (10%), ages 73 and 75, died of infection before engraftment and were unable to undergo response assessment. Two more patients, ages 70 and 73, died within or shortly after 100 days of treatment related complications (infection and cardiac arrhythmia), for a total of 4 (19%) early treatment related deaths (TRM). At median follow up of 25 months (range 7 48 months), median progression free survival (PFS) was 8 months (Fig. 1A) and median overall survival (OS) was 18 months (Fig. 1B). Ten patients (48%) survived in remission for at least 1 year following transplant.

Eight patients were alive at last follow up, of whom 7 remained in remission, while 13 patients had died. Of the eight deaths that occurred within the first year, four patients died of TRM and four died due to progressive lymphoma. Five deaths occurred more than 1 year after transplant: two patients died of progressive lymphoma, one died of unknown causes, one died of secondary AML at 3 years, and one died of intracranial hemorrhage 4 years following transplantation.

Progression free survival was superior in younger patients when compared to those 75 and older ($P = 0.004$). However, although there was a trend to better overall survival in younger patients, this trend did not reach statistical significance ($P = 0.084$). Conditioning regimen was not predictive of either PFS or OS. There was no association between CD34+ cell dose, time to neutrophil engraftment, or time to platelet engraftment and either PFS or OS.

HCT CI and CCI were calculated for all patients (Table II). Using the HCT CI, three patients were of high risk, eight patients were intermediate risk, and ten patients were low risk. Using the CCI, one patient was of high risk,

TABLE I. Demographics

Age: median (range)	71 (69 86)
69 70	9
71 74	7
75 86	5
Gender	
Male	13
Female	8
Histology	
DLBCL	13
Transformed	3
Burkitt	2
PTCL	1
FL	1
HL	1
Disease status	
Second remission	16
Third or greater remission	2
Primary refractory	2
First complete remission	1
CCI	
Low risk	13
Intermediate risk	7
High risk	1
HCT-CI	
Low risk	10
Intermediate risk	8
High risk	3

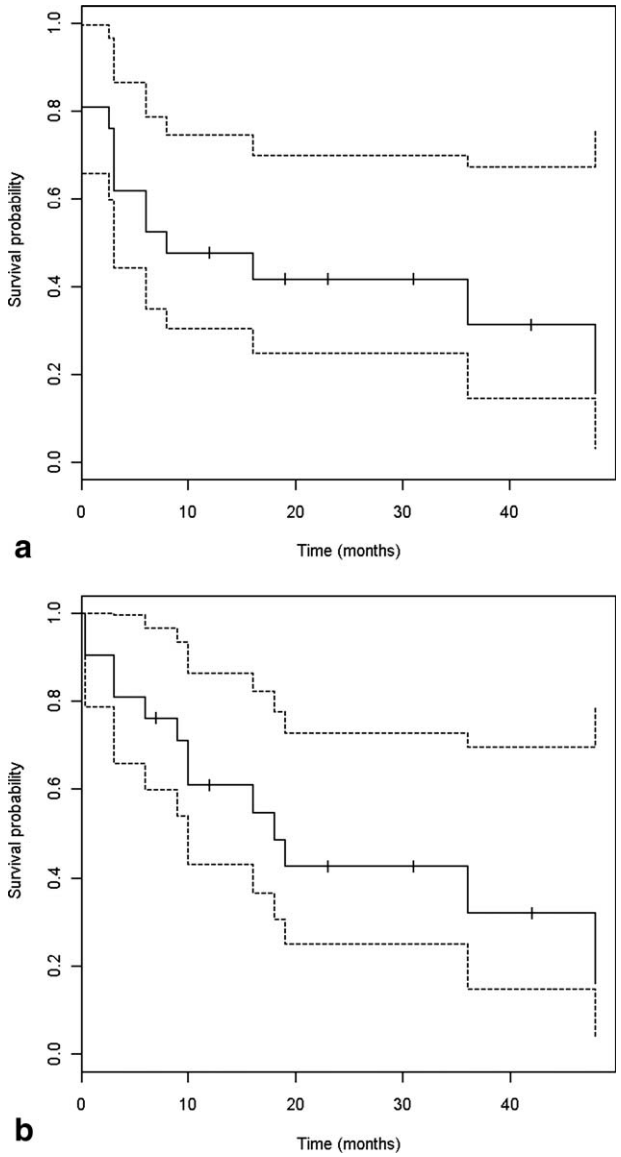

Figure 1. (A) Progression free survival for all patients. (B) Overall survival for all patients.

seven had intermediate risk, and thirteen were low risk. Considering the four patients who died within 100 days of TRM, three were high risk by HCT CI, and one was low risk, whereas using the CCI, one patient was considered high risk, two intermediate risks, and one low risk. Although there was no difference in OS between low and intermediate risk patients by either index, patients determined to be high risk by HCT CI experienced extremely poor survival, as shown in Fig. 2 (median 0.3 months vs. 19 months for nonhigh risk patients, $P = 0.000005$). Only one patient was identified to be high risk by CCI, limiting the predictive utility of this index.

In summary, we sought to assess the feasibility of ASCT for lymphoma in a group of very elderly patients and to evaluate the utility of pretransplant validated comorbidity assessments to predict outcome. Our data show that autologous stem cell transplantation is feasible and of potential benefit in selected very elderly patients with lymphoma.

Others have studied the impact of age on toxicity and mortality in the setting of stem cell transplantation. Although some have reported increased toxicity and/or TRM in patients over 60 as compared to younger patients [1,8 10], others have not observed this difference [2 5]. Two previous reports have evaluated the impact of comorbidities on out come in older patients undergoing ASCT. Wildes et al. [2] compared 59 patients aged 60 and older to younger patients, showing no difference overall in DFS or OS, but a significant impact of CCI on TRM and OS. Hosing et al. [3] found that, in patients over age 65 undergoing ASCT, HCT CI predicted for increased toxicity during transplant, but had no impact on OS.

Andorsky et al. recently published the first data of which we are aware evaluating ASCT in lymphoma patients 70 years of age and older [11]. In this small group of 17 patients, 1 year nonrelapse mortality was 35%. CCI and HCT CI were calculated but were not predictive for survival in this group. No pretransplant characteristics were identified that could help identify patients who would be at prohibitively high risk of this procedure.

HCT CI was predictive of survival in the group of patients presented here, supporting previous reports in younger patients that comorbidities are likely a more important factor in determining potential benefit of transplant than age. Although it is not clear why our results differ from those of Andorsky et al., it is possible that it relates to either the very small sample size or lack of inclusion of higher risk patients in the Andorsky report. In our small cohort, the HCT CI was more sensitive than the CCI in capturing high risk patients. In fact, 3 out of 4 (75%) patients who died within 100 days of trans plant were identified as high risk by the HCT CI. This could be the basis for testing the validity of the HCT CI in ASCT in elderly patients, and possibly across all age groups.

Within this elderly population, when patients 75 and older were compared to those $<$74 years of age, lymphoma specific outcomes appeared inferior. This finding suggests that, although ASCT appears to be tolerable in the setting of limited comorbidity, it may be less effective therapy for this older group of patients. Given the limited numbers and lack of statistical power, firm conclu sions regarding the impact of age alone will require a larger sample size.

We recognize several limitations to our study, including the retrospec tive nature of the data collection with potential associated selection bias, the fact that it is a single institution experience, and the small sample size, limiting firm conclusions regarding association of clinical factors with outcome. Notwithstanding these shortcomings, our findings extend ASCT as a feasible option in a selected group of very elderly patients. The paucity of published data addressing aggressive treatment options in this age group calls for more effort to discern patients who can bene fit from this approach.

In conclusion, age alone need not be an exclusionary factor for ASCT in elderly patients with lymphoma. Selected patients with limited comorbidities can benefit from this treatment modality in spite of advanced age.

Methods

We identified all patients age 69 or greater with a diagnosis of Hodgkin lymphoma (HL) or non Hodgkin's lymphoma (NHL) who underwent ASCT between June 2003 and December 2009. Patients were identified by review of the stem cell transplant database at Weill Cornell Medical College. Age,

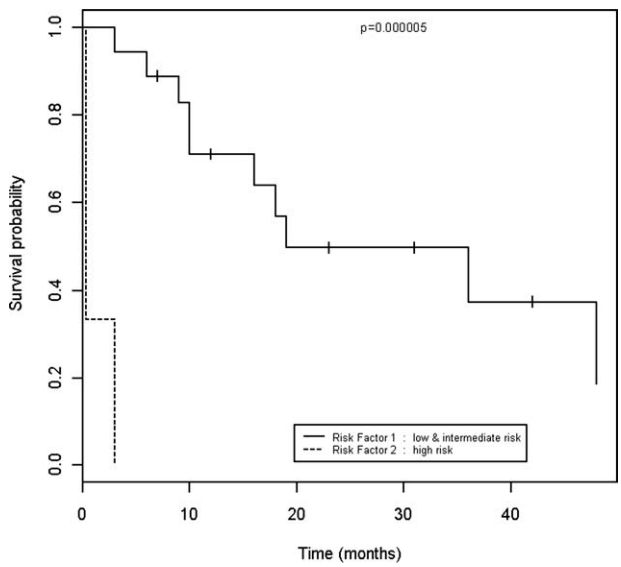

Figure 2. Kaplan Meier estimate of overall survival by HCT CI (risk factor 1: low and intermediate versus 2: high risk). Patients of high risk by HCT CI have inferior overall survival when compared to those of low or intermediate risk ($P = 0.000005$).

date of transplant, conditioning regimen, engraftment data (neutrophils and platelets), response, and survival data were derived from review of medical records. Determination of candidacy for ASCT and conditioning regimen were at the discretion of the treating physician.

Baseline Charlson comorbidity risk index (CCI) and hematopoietic stem cell transplant comorbidity index (HCT CI) were calculated for all patients. Comorbidity data were collected from review of medical records, and comor bidities were scored as previously published [6,7]. For both indices, a score of 0 was defined as low risk, a score of 1 2 was defined as intermediate risk, and a score of 3 or higher was considered high risk. Comorbidity risk scores were correlated with NRM, OS, and PFS.

Primary endpoints for the analysis were progression free survival (PFS) and overall survival (OS). OS was defined as the time from transplant until death or last follow up, and PFS was defined as the time from transplant until dis ease progression, death or last follow up. Treatment related mortality (TRM) was defined as death within 100 days of transplant not attributed to progres sion of lymphoma. Analyses of OS and PFS were performed using the Kaplan Meier method [12]. Confidence intervals were computed using a 95% confidence level. Confidence intervals for the median survival times were com puted using Brookmeyer and Crowley method [13]. Analysis was carried out using R A language and environment for statistical computing [14].

This study was reviewed and approved by the Investigational Review Board of Weill Cornell Medical College.

References

1. Jantunen E, Itala M, Juvonen E, et al. Autologous stem cell transplantation in elderly (>60 years) patients with non Hodgkin's lymphoma: A nation wide analysis. Bone Marrow Transplant 2006;37:367 372.
2. Wildes TM, Augustin KM, Sempen D, et al. Comorbidities, not age, impact outcomes in autologous stem cell transplant for relapsed non Hodgkin lym phoma. Biol Blood Marrow Transplant 2008;14:840 846.
3. Hosing C, Saliba RM, Okoroji G J, et al. High dose chemotherapy and autol ogous hematopoietic progenitor cell transplantation for non Hodgkin's lym phoma in patients >65 years of age. Ann Oncol 2008;19:1166 1171.
4. Jantunen E, Canals C, Atta M, et al. Autologous stem cell transplantation in patients with mantle cell lymphoma beyond 65 years of age:a study from the European Group for Blood and Marrow Transplantation (EBMT). Ann Oncol 2012;23:166 171.
5. Buadi FK, Micallef IN, Ansell SM, et al. Autologous heamatopietic stem cell transplantation for older patients with relapsed non Hodgkin's lymphoma. Bone Marrow Transplant 2006;37:1017 1022.
6. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prog nostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 1987;40:373 383.
7. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT) specific comorbidity index: A new tool for risk assessment before allo geneic HCT. Blood 2005;106:2912 2919.
8. Jantunen E, Mahlamaki E, Nousiainen T. Feasibility and toxicity of high dose chemotherapy supported by peripheral blood stem cell transplantation in eld erly patients (=60 years) with non Hodgkin's lymphoma: Comparison with patients <60 years treated within the same protocol. Bone Marrow Transplant 2000;26:737 741.
9. Kusnierz Glaz CR, Schlegel PG, Wong RM, et al. Influence of age on the outcome of 500 autologous bone marrow transplant procedures for hemato logic malignancies. J Clin Oncol 1997;15:18 25.
10. Mileshkin LR, Seymour JF, Wolf MM, et al. Cardiovascular toxicity is increased, but manageable, during high dose chemotherapy and autologous peripheral blood stem cell transplantation for patients aged 60 years and older. Leuk Lymphoma 2005;46:1575 1579.
11. Andorsky DJ, Cohen M, Naeim A, Pinter Brown L. Outcomes of auto SCT for lymphoma in subjects aged 70 years and over. Bone Marrow Transplant 2011;46:1219 1225.
12. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457 481.
13. Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982;38:29 41.
14. R Development Core Team.R: A Language and Environment for Statistical Computing. Vienna, Austria:R Foundation for Statistical Computing; 2011. Available at: http://www.R project.org.