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Autologous

Age over Fifty-Five Years at Diagnosis Increases Risk of Second Malignancies after Autologous Transplantation for Patients with Hodgkin Lymphoma

Sai Ravi Pingali [1], Rima M. Saliba [2], Paolo Anderlini [2], Chitra Hosing [2], Issa Khouri [2], Amin M. Alousi [2], Yago Nieto [2], Muzaffar H. Qazilbash [2], Richard Champlin [2], Uday R. Popat [2,*]

[1] *Houston Methodist Hospital, Houston, Texas*
[2] *The University of Texas MD Anderson Cancer Center, Department of Stem Cell Transplantation and Cellular Therapy, Houston, Texas*

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A B S T R A C T

The impact of age at diagnosis on outcomes of patients with Hodgkin lymphoma (HL) undergoing autologous hematopoietic transplantation (auto-HCT) is unclear. We retrospectively evaluated the impact of age on outcomes of 310 consecutive patients with relapsed/refractory HL who underwent auto-HCT between January 1996 and December 2010 with carmustine, etoposide, cytarabine, and melphalan conditioning therapy. Patients were stratified into ≤ 55 and >55-year-age groups based on age at diagnosis. At a median follow-up of 80 (range, 1 to 180) months, progression-free survival was similar between both age groups. However, age older than 55 years at diagnosis was associated with significantly poor overall survival with a hazard ratio [HR] of 2.3 ($P = .003$) from higher rate of second malignancies (HR, 3.8; $P = .015$) compared with patients 55 years or younger. In conclusion age > 55 years at diagnosis increases risk of second malignancies after auto-HCT.

BACKGROUND

Age at diagnosis is of prognostic significance in both early and advanced-stage Hodgkin lymphoma (HL). Age of 45 years and older is an independent prognostic factor for freedom from progression for patients with advanced HL. Similarly, age of 50 years and older is considered to be an unfavorable feature in studies of early-stage HL conducted by cooperative groups [1-4]. Despite improved long-term outcomes in patients with HL in last few decades, survival outcomes decline with each decade of advancing age. Estimated 5-year progression-free survival (PFS) of 80% and overall survival (OS) of 90% for patients younger than 60 years, compared with PFS of 60% and OS of 65% for patients older than 60 years, is due to high-risk disease, excessive toxicities, and suboptimal therapy [5-7]. Two randomized trials and multiple other studies that showed improved disease-free survival led to use of high-dose chemotherapy (HDC) with carmustine, etoposide, cytarabine, and melphalan (BEAM) as a standard consolidation therapy [8-18].However, these studies did not include patients older than 60 years, and eligible elderly patients receive HDC and auto-HCT based on feasibility and safety data on auto-HCT for patients with non-Hodgkin lymphoma [19,20].

There is conflicting data on the impact of age on outcomes of auto-HCT for patients with relapsed and refractory HL. Some auto-HCT studies that included age in the prognostic scoring model show inferior outcomes with increasing age [21-23]. Other studies, which included age as an independent prognostic factor, concluded that age was not a negative factor [24,25]. Often, these studies only evaluated PFS, and OS was not reported. We retrospectively analyzed outcomes of 310 consecutive patients with relapsed/refractory HL receiving auto-HCT at our institution with an objective of determining the impact of age on the outcomes.

PATIENTS AND METHODS

Institutional review board approval for human subjects' research was obtained for this retrospective study. All consecutive patients who underwent auto-HCT for relapsed/refractory HL between January 1996 and December 2010 at MD Anderson Cancer Center were included in this study. All patients received institutional standard BEAM conditioning and were mobilized with ifosfamide and etoposide regimen. Standard supportive care and antibiotic prophylaxis were used for all patients. Patient- and disease-specific characteristics of age, gender, number of chemotherapy regimens received, exposure to radiation therapy, and response to chemotherapy before transplantation were collected. Based on bimodal age distribution of HL with a peak between the ages of 15 and 34 years with peak incidence at 25 years

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* Correspondence and reprint requests: Uday R. Popat, MD, The University of Texas MD Anderson Cancer Center, Department of Stem Cell Transplantation and Cellular Therapy, 1515 Holcombe Blvd # 853, Houston, TX 77030.
E-mail address: upopat@mdanderson.org (U.R. Popat).

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and second peak after the ages 50 to 55 years, we stratified patients into 3 groups based on age at diagnosis: older than age 55, 26 to 55 years of age, and 25 years of age and younger [26-28]. However, given that the characteristics and outcomes were similar between the groups of patients 25 years or younger and patients between 26 and 55 years, these groups were merged to increase the statistical power and were compared against age >55 years group.

Study Endpoints

The primary objective of this study was to evaluate OS, PFS, and nonrelapse mortality (NRM) of older patients with relapsed HL receiving auto-HCT. The secondary objective of this study was to determine causes of NRM in patients with relapsed HL receiving auto-HCT.

Statistical Analysis

Baseline patient- and disease-related characteristics were compared using the chi-square test for categorical variables and Mann Whitney's rank-sum test for continuous variables. Actuarial OS was estimated using the Kaplan-Meier method. The cumulative incidences of disease progression, NRM, and of second malignancies were estimated accounting for competing risks. Death before the occurrence of the respective events was considered a competing risk for disease progression and second malignancy. Progression of malignancy and death with disease were considered competing risks for NRM. Prognostic factors for OS, disease progression, NRM, and second malignancies were assessed on univariate analysis using Cox proportional hazards regression analysis. Multivariate analysis using Cox regression was performed to assess prognostic factors for OS. Statistical significance was determined at .05 level. Statistical analysis was performed using STATA 11 (Stata Statistical Software: Release 11. StataCorp LP, College Station, TX).

Table 1
Patient Characteristics

Characteristics	Age at Diagnosis		*P* Value
	>55 (n = 30)	≤ 55 (n = 280)	
Diagnosis to transplantation, median (range), mo	19 (5-75)	24 (6-346)	.05
Age at transplantation, yr			
≤55	0 (0)	274 (98)	
>55	30 (100)	6 (2)	
Male	22 (73)	153 (55)	.05
Disease status			
CR/CRU	8 (27)	92 (33)	.80
PR	18 (60)	154 (55)	
SD/PD	4 (13)	34 (12)	
No. of prior chemotherapy regimens			
≤3	26 (87)	222 (79)	.20
>3	4 (13)	58 (21)	
MOPP chemotherapy	0 (0)	20 (9)	
Histology at diagnosis			
Nodular sclerosis	20 (67)	236 (84)	.02
Other	10 (33)	44 (16)	

Data presented are n (%) unless otherwise indicated.
CR indicates complete remission; CRU, complete remission unknown; PR, partial remission; SD, stable disease; PD, progressive disease.

RESULTS

A total of 310 patients with relapsed/refractory HL underwent auto-HCT during the study period with BEAM conditioning. Among these patients, 30 (10%) were older than age 55 (range, 56 to 73) with median age of 60, and 280 patients (90%) were 55 (range, 9 to 55) years or younger with median age of 27 at the time of diagnosis. The vast majority of patients (256; 82.6%) had nodular sclerosis–type HL and over 98% of patients received peripheral hematopoietic cell transplantation. Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) was the most common frontline therapy (284; 91.6%); 20 patients received meclorethamine, vincristine, procarbazine, and prednisone (MOPP); and the frontline therapy was unknown in 6 patients. All patients who received MOPP chemotherapy were <55 years old. Characteristics of the study population were stratified according to age (≥55 years and <55 years) and are described in Table 1.

Patients older than age 55 and those 55 years or younger were compared according to gender, disease status, histology, number of prior therapies, and cause of death. The distribution of patients according to disease status at transplantation was comparable in older and younger patient groups, with the majority of patients having achieved a partial response before transplantation. The number of lines of prior chemotherapies was also similar between the 2 groups. Twenty-one percent of those older than age 55 had received more than 3 lines, compared with 13% of those ages 55 and younger ($P = .20$). MOPP chemotherapy was frontline therapy in 20 patients, all of whom were <55 years of age. In both groups, the majority of patients were male, with a marked predominance in the 55-and-older group (73% versus 55%; $P = .05$). At a median follow-up of 80 (range, 1 to 180) months, outcomes for the entire patient cohorts according to age are as described in Table 2.

OS

Age at diagnosis, age at auto-HCT, response before auto-HCT, and number of prior chemotherapy regimens were the only significant factors predicting OS on univariate analysis. Gender, prior radiation therapy, and disease histology (nodular sclerosis versus others) did not significantly affect outcomes. OS at 80 months was 65% for the entire cohort, 69% in 55-and-younger group, and 27% in the older-than-55 years group ($P = .003$). Patients who only achieved partial remission or had stable disease/progressive disease at the time of auto-HCT were at higher risk for mortality than patients who were in complete remission, with hazard ratios [HRs] of 1.7 (95% confidence interval [CI], .98 to 2.8; $P = .06$) and 4.5 (95% CI, 2.4 to 8.4; $P < .001$), respectively. The number of prior therapies also influenced OS, and patients receiving more than 3 prior regimens had a mortality HR of 1.7 (95% CI, 1.1 to 2.7; $P = .02$). Factors that were significant on univariate analysis, age at diagnosis, disease status before auto-HCT, and number of prior regimens, were included on multivariate analysis. Only age older than 55 years at diagnosis (HR, 2.3; 95% CI, 1.3 to 3.9; $P = .003$) and response before auto-HCT (HR, 2.9;

Table 2
Outcomes of Autologous Hematopoietic Transplantation at Median Follow-Up of 80 Months Based on Age at diagnosis

Outcomes	Entire Cohort	>55 Years n = 30	≤ 55 Years n = 280	*P* Value
OS	65% (59-71)	27% (9-49)	69% (63-74)	.003
PFS	54% (48-60)	31% (12-53)	56% (50-62)	.20
CI of progression	38% (33-44)	41% (26-64)	37% (32-44)	.70
CI of NRM	8% (5-12)	33% (16-65)	5% (3-9)	.001
CI of second malignancy	11% (7-16)	30% (16-57)	8% (5-14)	<.001
CI of second malignancy excluding skin cancers	9% (6-13)	22% (10-49)	7% (4-12)	.003

CI indicates cumulative incidence.