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Survivorship after Autologous Hematopoietic Cell Transplantation for Lymphoma and Multiple Myeloma: Late Effects and Quality of Life

George E. Georges, MD[1,3], **Merav Bar, MD**[1,3], **Lynn Onstad, ScM**[1], **Jean C. Yi, PhD**[2], **Mazyar Shadman, MD, MPH**[1,3], **Mary E. Flowers, MD**[1,3], **Paul A. Carpenter, MD**[1,3], **Susan Stewart**[4], **Stephanie J. Lee, MD, MPH**[1,3], **Leona A. Holmberg, MD, PhD**[1,3]

[(1)]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[(2)]Biobehavioral Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

[(3)]Medicine/Medical Oncology, University of Washington, Seattle, WA

[(4)]Blood & Marrow Transplant Information Network, Highland Park, IL

Abstract

Although autologous hematopoietic cell transplantation (AHCT) is standard therapy for patients with lymphoma and multiple myeloma (MM), few studies have addressed late effects and quality of life (QOL) for long-term survivors after AHCT. Using long-term follow-up (LTFU) annual questionnaires with self-reported outcomes, we surveyed 665 patients who were ≥5 years after AHCT for the diagnosis of lymphoma or MM. Three-hundred and eighty-nine patients completed the questionnaire (58% response rate) a median of 11 (range 5-30) years after AHCT. The median age (years, range) among 268 lymphoma patients was 63 (22-88), and for 121 multiple myeloma patients was 69 (34-84). The most commonly reported medical conditions (>10% incidence) included: sexual dysfunction, history of shingles, cataracts, osteoporosis or osteopenia, joint replacement, and skin cancer. Current medication use was more frequent in MM patients for: infection prevention/treatment (19% multiple myeloma vs 5% lymphoma, p<.001), hypertension (41% vs. 26%, p=.004), osteoporosis (23% vs. 10%, p=<0.001), and pain (33% vs. 11%, p<.001). Treated hypothyroidism was more common in lymphoma patients. In multivariate analysis combining lymphoma and MM, worse physical functioning was associated with older age, shorter time since AHCT, comorbidities, relapse and treatment for depression and/or pain. Worse mental functioning was associated with younger age and treatment for anxiety, depression

Corresponding author: George E. Georges, MD, Associate Member, Fred Hutchinson Cancer Research Center, Associate Professor, University of Washington, 1100 Fairview Ave. N, D1-100, Seattle, WA 98109-1024, Phone: 206.667.6886, Fax: 206.667.6124, ggeorges@fredhutch.org.

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Conflict of interest

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or pain. In conclusion, AHCT survivors report generally good QOL but many late effects and symptoms that are potentially amenable to intervention.

Keywords

autologous hematopoietic cell transplantation; lymphoma; multiple myeloma; late effects; quality of life

Introduction

Allogeneic hematopoietic cell transplantation (HCT) is well known to be associated with significant late effects after transplantation, but autologous transplant (AHCT) survivors also have a high burden of comorbidities based on studies with shorter follow-up or in younger patients.[1-3] Autologous HCT is associated with higher mortality rates than the general population due primarily to relapsed malignancy.[4-9] Recent trends in the annual number of AHCTs reported in North America and Europe indicate a slowly increasing number of patients with lymphoma and a much faster increase in the number of patients with MM undergoing AHCT.[10] Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) show an increase in survival after AHCT for MM,[10] resulting in an increasing number of AHCT survivors. Although some data have been published about the late effects in lymphoma survivors after AHCT,[2,5,6,8,11,12] data addressing long-term effects in MM AHCT patients is lacking in the era of novel agent therapy. Knowledge about important medical conditions and quality of life (QOL) deficits that affect long term survivors would help inform appropriate counseling and monitoring strategies.

To study the health of long-term survivors, we surveyed patients who were 5 years or more after AHCT for lymphoma and MM with long term follow up (LTFU) questionnaires. We studied these patient populations since both primarily received high dose chemotherapy-based preparative regimens and autologous cell infusions, but differ in their pre and post-transplant disease therapy and management. These groups also are the largest populations of survivors after AHCT. These data provide a comprehensive assessment of the key medical and QOL issues facing patients who are LTFU survivors after AHCT.

Materials and Methods

Patients.

Between July 2015 to September 2017, annual questionnaires were sent to 665 patients who were ≥5 years after AHCT for the diagnosis of lymphoma or MM who had received AHCT at a single center (Fred Hutchinson Cancer Research Center (FHCRC)/ Seattle Cancer Care Alliance) in Seattle, WA. Syngeneic transplant recipients and patients who subsequently underwent allogeneic transplant were excluded. Patients may have had two AHCT procedures as long as the most recent one was 5 or more years ago.

Surveys.

The questionnaires were approved by the FHCRC Institutional Review Board, and all participants provided written informed consent. The questionnaire consisted of the short form 36 (SF-36), focusing on physical and mental QOL[13,14] and questions about the medical conditions ever experienced and current medications taken by respondents. Respondents indicated whether they had any medical conditions by checking Yes, No, or Don't know/not applicable, for example, "pulmonary embolism or clots in legs or arms," "osteoporosis or osteopenia (thin bones)," and "seizure." Medication use was captured by endorsement of taking classes of drugs for specified indications, such as "high blood pressure," "prescription medications for pain," and "depression." The QOL instrument, the SF-36, allows calculation of a physical component score (PCS) and a mental component score (MCS) that reflect physical and mental functioning. Scores are normalized so the general population median is 50 with a standard deviation of 10 points. The questionnaires did not ask if patients received maintenance chemotherapy post AHCT or whether they were still on maintenance therapy when answering the questionnaires. No pre-AHCT medical history or family history was available. Follow-up questionnaires with a reminder letter were sent to patient addresses after 4 weeks if no reply was received. The most recent survey was analyzed if respondents replied to more than one questionnaire. Respondents could participate in the survey by completion of printed documents sent via US postal service or by internet web-based interface. Since the majority of surveys were returned by mail over a period of time, we do not know who responded to the initial contact versus the reminder. Incomplete surveys were analyzed for the data provided, and there was no extrapolation for missing or incomplete data. Copies of the survey are available by contacting the corresponding author at LTFU@fredhutch.org.

Biostatistical analysis.

Participant characteristics, self-reported medical conditions, and self-reported medications were tabulated and compared between lymphoma and MM patients using Chi squared test for categorical variables, Wilcoxon rank sums test/Kruskal Wallis test for comparing medians of continuous variables, and ANOVA for comparing means of continuous variables. Multivariate linear regression was used to identify associations between the outcomes of SF-36 physical and SF-36 mental summary scores and factors of age, sex, years since transplant, comorbidities, relapse, and medications for anxiety, depression, sleep, and pain; factors found to be associated were examined for interactions using stepwise regression with model entry and exit criteria of $p=0.05$.

Results

There were 665 survivors transplanted for lymphoma and MM who survived 5 or more years after AHCT who were sent at least one survey during the study. Of these, 389 responded (58%) with a similar response rate between lymphoma and MM. (Table 1) There were 268 patients with lymphoma (68.9%) (55 with Hodgkin lymphoma and 213 with non-Hodgkin's lymphoma) and 121 patients with multiple myeloma (31.1%). Exploratory analysis showed that Hodgkin lymphoma patients were more likely to be female (55% vs. 37%, $p=0.019$) and younger (median 52.1 vs. 65.5 years, $p<0.001$), and to receive high dose total body

irradiation (TBI, 42% vs. 27%, p=0.03) compared to non-Hodgkin's lymphoma. None of the medical complications or medication usage differed between the Hodgkin and non-Hodgkin lymphoma groups at p<0.01 (data not shown), thus they were combined for presentation and analysis. Overall, 103 (26.5%) responded online while the rest completed paper surveys. The proportion who completed the survey online was similar between MM and lymphoma (p=0.13).

Patients transplanted for lymphoma were more likely to receive bone marrow (12% vs. 0%, p<.001) and high dose TBI in the conditioning regimen (36% vs. 2%, p<.001), less likely to be a racial/ethnic minority (7% vs 16%, p=0.005), and to be slightly younger (median 63 vs. 69, p<.001) and longer after AHCT (median, 12.0, range 5.9-30.0 vs. median, 8.0, range, 5.0-24.9, p<.001) than patients with MM. Ten percent of lymphoma and 13% of myeloma respondents had relapsed after AHCT. Patients transplanted for lymphoma reported better physical functioning (p=0.017) and were more likely to be working or in school full or part time p=0.006. These differences were not due to the differences in time since AHCT. Adjusting for age attenuated the SF-36 physical component score differences and abrogated the differences in work/school status.

Table S1 (supplemental material) summarizes the key factors (as defined in Table 1) compared between non-responders and responders to the questionnaire. Survey responders were older at the time of the survey (median 65 vs. 63 p=.004) than non-respondents, less likely to be a racial/ethnic minority (10% vs 17%, p=0.007), and longer after AHCT (median, 10.9, range 5.0-30.0 vs median, 9.9, range 5.9-29.9, p=0.013). Otherwise there were no significant differences in sex, graft source, conditioning regimen, disease, and post-AHCT relapse between respondent groups.

Table 2 shows the medical conditions as reported by all responders to the questionnaire. The most common reported medical conditions with greater than 10% incidence were the following: Sexual dysfunction, history of shingles, cataracts, osteoporosis or osteopenia, joint replacement, and skin cancer. Significant differences between lymphoma and MM patients after AHCT were identified for several medical conditions (Tables 2 and 3). Lymphoma survivors were more likely to report post-traumatic stress symptoms (6% vs. 1%, p=0.019) whereas MM patients were more likely to report spontaneous bone fracture/ compression (5% lymphoma vs. 18% MM, p<0.001). Notable medical conditions that were not different between patients with lymphoma and MM included myocardial infarction or angina, stroke, congestive heart failure, pulmonary embolism/clots or kidney failure requiring dialysis.

Table 3 shows the medications currently taken by all patients for a variety of medical conditions. The most frequently reported use of medications (≥20% among patients with MM or lymphoma) were for the following conditions: High blood pressure, heartburn or reflux, high cholesterol, sleep problems, thyroid replacement, pain, muscle cramps, prevention or treatment of osteoporosis, and hormone replacement therapy. Patients transplanted for MM were more likely to be taking medication for infection prevention/ treatment (p<0.001), hypertension (p=0.004), osteoporosis (p<.001), pain (p=<.001), and heartburn/reflux (p=0.031). Lymphoma patients were more likely to be on thyroid hormone

replacement therapy, p<.001. Surprisingly, among lymphoma patients, TBI use was associated with a lower likelihood of taking thyroid replacement (19.5% vs. 50%, p<0.001) with no difference between Hodgkin and non-Hodgkin's lymphoma.

Physical and mental functioning were minimally correlated with each other (Spearman correlation =0.22). Twenty-seven percent of lymphoma patients had a low PCS more than 1 STD below the general population compared with 41% of MM patients (p=0.004) while the proportion with low MCS was the same (13%). Median SF36 PCS were lower in patients transplanted for MM (44.5 vs. 49.1). Combining lymphoma and MM patients, Table 4 shows correlates of PCS and MCS in 358 (92.0%) patients by multivariate analysis of responses to the SF-36 instrument. Parameter estimates (PE) that are positive integers indicate a positive association with PCS or MCS while negative integers indicate a negative association with PCS or MCS. In multivariate analysis, higher PCS was associated with younger age at time of questionnaire or AHCT (p=.029), no treatment for depression (p=.003), no comorbidities (p<.001), and no treatment for pain (p<.001), however the effect was attenuated for those with a comorbidity who had treatment for pain (p<.001). Better mental health was associated with older age (p<.001) and no medication for anxiety (p<.001), or depression (p<.001).

Discussion

This is one of the most comprehensive reports of late outcomes among AHCT survivors transplanted for lymphoma and MM. We used LTFU annual surveys with health questionnaires over a two-year time period to assess the incidence of medical conditions and complications and the physical functioning and mental health among a large cohort of LTFU survivors who were 5 or more years after AHCT.

We identified several key differences and similarities in late effects and QOL between patients with lymphoma and MM. Overall, lymphoma patients reported better health and QOL. Several conditions and complications may be explained by disease-specific complications unique to MM. For example, as MM is frequently associated with multiple lytic bone lesions, as expected the incidence of osteoporosis and bone fractures/compression and use of pain medication was more frequent in this population. We did not collect data on use of maintenance therapy post AHCT and do not know how its use impacted the development of the late effects seen. As many patients with MM are now treated long term with maintenance chemotherapy such as lenalidomide to prevent disease relapse after AHCT, this may also explain the greater incidence of antibiotic use for infection prevention/ treatment and other effects among MM patients compared to lymphoma. Although MM patients were slightly older than lymphoma patients and were transplanted more recently, we did not find evidence that these factors could explain the observed differences.

The use of TBI transplant conditioning was more frequent in patients with lymphoma. Although lymphoma patients had a higher incidence of hypothyroidism than MM patients, within the lymphoma population, patients receiving TBI paradoxically had a lower incidence of hypothyroidism. Other medical conditions did not differ between lymphoma and MM survivors such as cardiac conditions, which might have been expected to be higher in lymphoma survivors because of anthracycline exposure[15] or total body irradiation.

Thromboembolic events, which might be expected to be higher in MM survivors because of exposure to immune modulatory drugs (IMiDs)[16] was not different between the groups. The most frequent symptom reported by more than 50% of survivors in both groups was sexual dysfunction, suggesting the need for effective interventions.

Other factors unrelated to the disease may account for some of the observed differences between lymphoma and MM patients. For example, increased age is associated with an increased incidence of hypertension in the general population. The increased median age for patients with MM among the patients in our study may explain the increased incidence of hypertension among MM patients.

Other outcomes of the survey do not have an obvious causal or likely explanation. Although uncommon in both groups, the proportion of lymphoma patients with post-traumatic distress symptoms was higher than the MM group. Myeloma patients primarily undergo AHCT to prolong disease-free survival and anticipate disease relapse whereas lymphoma patients are hoping to be cured and may worry more about relapse. In fact, 10% of lymphoma patients and 13% of multiple myeloma patients reported post-transplant relapse, which was a risk factor for worse patient physical functioning. Relapse has been associated with worse caregiver mental functioning[17] and a higher risk of patient suicide.[18] Interestingly, we did not see differences in mental functioning between those who relapsed and were surviving and those who never relapsed. This may be partially explained by the fact that MM and lymphoma patients with aggressive disease will succumb to complications of their disease within two years after relapse so that those who relapse and are able to respond to the survey may have more indolent or treatable disease.

The 9% incidence of prior or current smoking or chewing tobacco among AHCT survivors is important. While rate is lower than the general population, it is still too high for survivors at risk of tobacco-related complications. Obstructive and restrictive lung disease and decreased cardiorespiratory fitness have been seen in AHCT survivors.[11,19] The use of tobacco after high dose myeloablative chemotherapy is associated with an increased incidence of secondary malignancies such as cancers of the lung and digestive tract. Clearly more aggressive medical interventions such as smoking cessation counselling and education or pharmaceutical treatment for those still smoking can result in a lower incidence of tobacco use and a lower incidence of complications associated with tobacco use.

Overall, 32% of patients with MM reported use of pain medications and 22% of all patients reported use of medications to treat anxiety and/or depression. The use of such medications was associated with worse functional status. Patients with these conditions after AHCT may benefit from more intensive treatment of the underlying conditions. This may take the form of physical therapy and exercise, or psychiatric treatment and counselling, with the goal of successfully treating depression, anxiety or pain in order to allow patients to improve both physical function and mental health.

There are a number of limitations to our study, including that we are missing some key information that would have enriched our understanding of late effects and QOL. Some important symptoms, such as cognitive functioning and fatigue, and current disease status

were not captured at the time of the survey, and no pre-AHCT patient-reported outcomes were collected so we do not know if deficits preceded AHCT. We also do not have information on whether patients were taking maintenance therapy to try to prevent relapse. We plan to start collecting this information.

With the higher documented rate of medical co-morbidities in survivors of autologous transplantation, screening and preventive measures assume greater importance.[20] Despite having survived a cancer and AHCT, many people continue to practice unhealthy habits that increase their risks for late treatment complications.[21,22] There are efforts to increase knowledge of[23] and compliance with published guidelines[24] to improve the health and well-being of survivors,[25,26] but to date evidence of their effectiveness in decreasing morbidity is lacking. Nevertheless, compliance with recommended screening (based on both disease-specific and general population considerations)[27,28] and prevention (immunizations and healthy habits)[21,29,30] seems wise. For example, the high rate of shingles suggests efforts to vaccinate AHCT survivors are warranted.

In summary, at a median of 11 (range, 5-30) years after AHCT, we have identified important late effects and QOL deficits that are potentially amenable to intervention. Targeted interventions to improve QOL and decrease late effects can contribute to the improved success of transplant therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- After autologous hematopoietic cell transplantation (AHCT), lymphoma patients reported better health and QOL compared to multiple myeloma.
- At a median of 11 years after AHCT, we identified important late effects and QOL deficits that are potentially amenable to intervention.

Table 1.

Participant characteristics

Characteristic		Lymphoma (N=268)	Myeloma (N=121)	P-value*
Current Age	Median years (Range)	63.4 (22.2-88.7)	68.9 (33.7-84.0)	<.001
Sex	Female	109 (41%)	59 (49%)	0.136
	Male	159 (59%)	62 (51%)	
Racial/ethnic minority (n=371)	Yes	18 (7%)	19 (16%)	0.005
Graft source	Bone marrow	32 (12%)	0 (0%)	<.001
	Peripheral blood	236 (88%)	121 (100%)	
High dose total body irradiation	Yes	80 (36%)	2 (2%)	<.001
Smoke or chew tobacco	Yes	21 (8%)	12 (11%)	0.469
Body mass index (n=369)	Underweight (<18.5)	5 (2%)	4 (3%)	0.237
	Normal (18.5-24.9)	99 (39%)	39 (34%)	
	Overweight (25-30)	101 (40%)	41 (35%)	
	Obese (>30)	49 (19%)	32 (28%)	
Relapse after transplant	Yes	28 (10%)	16 (13%)	0.424
Years since transplant	Median (Range)	12.0 (5.9-30.0)	8.0 (5.0-24.9)	<.001
Physical component score	<40	70 (27%)	45 (39%)	0.017
Mental component score	<40	40 (15%)	13 (11%)	0.302
Karnofsky performance status	≥80	228 (87%)	97 (82%)	0.188
Overall health	Excellent	43 (16%)	7 (6%)	0.058
	Very good	95 (36%)	42 (35%)	
	Good	84 (32%)	49 (41%)	
	Fair	39 (15%)	20 (17%)	
	Poor	5 (2%)	2 (2%)	
Work status	Working/school full or part time	117 (44%)	33 (27%)	0.006
	Retired	119 (44%)	73 (60%)	
	Other	32 (12%)	15 (12%)	
Response rate		268/456 (59%)	121/209 (58%)	0.831

*P-values are obtained from Chi-square test for categorical variables, Wilcoxon rank sum test/Kruskal Wallis test for comparing medians of continuous variables, and Anova for comparing means of continuous variables

Table 2.

Self-reported medical conditions

Medical condition	Lymphoma (n=268)	Myeloma (n=121)	p-value
Spontaneous (non-traumatic) bone fracture or spine compression	**13 (5%)**	**21 (18%)**	**<.001**
Osteoporosis or Osteopenia	54 (22%)	33 (30%)	0.081
Joint replacement	26 (10%)	18 (15%)	0.173
Avascular necrosis	6 (2%)	2 (2%)	1.000
Heart attack or angina, treated with medications, surgery, bypass surgery, or a stent	23 (9%)	11 (9%)	0.928
Stroke	14 (5%)	2 (2%)	0.095
Seizure	8 (3%)	1 (1%)	0.284
Congestive heart failure or cardiomyopathy	19 (7%)	8 (7%)	0.807
Pulmonary embolism or clots in legs or arms	21 (8%)	15 (13%)	0.175
Skin cancer	41 (16%)	17 (15%)	0.713
Another malignant neoplasm, not skin cancer	16 (8%)	4 (4%)	0.173
Pancreatitis (inflammation of the pancreas)	3 (1%)	2 (2%)	0.649
Kidney failure (requiring dialysis)	4 (2%)	5 (4%)	0.148
Cataracts	98 (38%)	52 (44%)	0.319
Post-traumatic stress disorder, requiring treatment	**16 (6%)**	**1 (1%)**	**0.019**
Problems with sexual desire, erection, ejaculation, vaginal dryness or pain	147 (62%)	58 (51%)	0.058
Varicella zoster virus (VZV) or shingles	104 (41%)	52 (44%)	0.545

Table 3.

Self-Reported Medications

Indication	Lymphoma (n=268)	Myeloma (n=121)	p-value
Abnormal heart rhythm	33 (13%)	9 (8%)	0.154
Hypertension	**68 (26%)**	**49 (41%)**	**0.004**
High blood sugar	35 (14%)	19 (17%)	0.434
High cholesterol or blood fat	85 (33%)	27 (24%)	0.069
Heartburn or reflux	65 (25%)	42 (36%)	0.031
Low thyroid	**111 (43%)**	**27 (23%)**	**<.001**
Low female or male hormone	49 (20%)	13 (12%)	0.090
Anxiety	40 (16%)	20 (17%)	0.758
Depression	35 (14%)	22 (19%)	0.214
Sleep problems	51 (20%)	29 (25%)	0.244
Prevention or treatment of osteoporosis	**25 (10%)**	**26 (23%)**	**<.001**
Swelling or edema	18 (7%)	7 (6%)	0.760
Muscle cramps	41 (16%)	27 (24%)	0.076
Prescription medication for pain	**28 (11%)**	**38 (32%)**	**<.001**
Inhaler or bronchodilator for breathing	33 (13%)	15 (13%)	0.959
Blood thinners to prevent or treat clots	36 (14%)	22 (19%)	0.208
Prophylactic antibiotics	**14 (5%)**	**22 (19%)**	**<.001**

Table 4.

Multivariate analysis of SF36 responses

	Physical Component Score		Mental Component Score	
	Parameter estimate*	**p-value**	**Parameter estimate***	**p-value**
Age	−0.10	0.029	0.24	<.001
Comorbidity and treatment for pain				
No co-morbidity, no treatment for pain	Ref			
At least one comorbidity, no treatment for pain	−5.23	<.001		
No-comorbidity, treatment for pain	−11.54	<.001		
At least one comorbidity, treatment for pain	−8.97	<.001	-	-
Treatment for depression	−4.27	0.003	−7.73	<.001
Treatment for anxiety	-	-	−6.48	<.001

* positive values indicate a positive correlation with better functioning