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Morbidity Burden in Multiple Myeloma Survivors of Autologous Transplant -a Bone Marrow Transplant Survivor Study (BMTSS)

Mukta Arora, MD, MS[1], **Yanjun Chen, MS**[2], **Lindsey Hageman, MPH**[2], **Jessica Wu, MPH**[2], **Wendy Landier, PhD**[2], **Liton Francisco, BA**[2], **Michelle Kung, MA**[2], **Emily Ness, MPH**[2], **Alysia Bosworth, BA**[3], **Merve Pamukcuoglu**[1], **Daniel J. Weisdorf, MD**[1], **Stephen J. Forman, MD**[3], **Saro H. Armenian, DO, MPH**[3], **Smita Bhatia, MD, MPH**[2]

[1]Division of Hematology, Oncology and Transplant, University of Minnesota, Minneapolis, Minnesota

[2]Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, Alabama

[3]Department of Population Sciences, City of Hope, Duarte, California.

Abstract

Background: Autologous blood or marrow transplantation (aBMT) is considered standard-of-care for multiple-myeloma (MM). Significantly improved survival necessitates an understanding of the morbidity burden borne by the growing survivor population.

Methods: We evaluated severe/ life-threatening chronic health conditions (CHCs) and subsequent neoplasms (SNs) in MM patients treated with aBMT using BMTSS. Study participants (n=630) had undergone aBMT for MM at one of 3 BMT centers, had survived ≥2y after aBMT, and were ≥18y of age at survey completion. aBMT survivors identified 289 nearest-age siblings to constitute an unaffected comparison group. Scoring of CHCs was based on CTCAE *v*5.0 to determine severity (grade 3: serious; grade 4: life-threatening).

Results: The 10y cumulative incidence of any grade 3–4 CHC in aBMT survivors was 57.6±3.2%. MM survivors were at 40% higher odds of developing grades 3–4 CHCs when compared with siblings (95%CI, 1.0–1.9). Amongst SNs, 96% were solid tumors, yielding a 10y cumulative incidence of 13.6±2.5%. Pre-aBMT exposure to cyclophosphamide (HR=3.5, 95%CI, 1.5–8.1) and immunomodulatory drugs (IMiDs, HR=3.9, 95%CI, 1.5–10.1) were associated with increased risk of solid tumors. Melanoma (10y cumulative incidence: 3.3%±1.2%), and squamous cell carcinoma (SCC: 10y cumulative incidence: 5.1%±1.8%), were the most common SNs. Pre-

Correspondence: Mukta Arora, MD, MS, Professor, Division of Hematology, Oncology and Transplantation, 420 Delaware Street SE, Minneapolis, MN 55455; Phone 612 626 4105; Fax: 612 625 6919; arora005@umn.edu.

Author contribution:

Mukta Arora: Concept and design, integrity of data and accuracy of data analysis; drafting and critical revision of the manuscript. **Yanjun Chen:** Integrity of data and data analysis; and critical revision of the manuscript. **Lindsey Hageman, Jessica Wu, Wendy Landier, Liton Francisco, Michelle Kung, Emily Ness, Alysia Bosworth and Merve Pamukcuoglu:** Administrative, technical support; acquisition, analysis, and interpretation of data; and critical revision of the manuscript. **Daniel J. Weisdorf, Stephen J. Forman and Saro H. Armenian:** Acquisition, analysis, and interpretation of data; and critical revision of the manuscript. **Smita Bhatia:** Concept and design, integrity of data and accuracy of data analysis; drafting and critical revision of the manuscript; acquisition of funding; supervision and administrative support.

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aBMT exposure to cyclophosphamide (HR=6.02, 95%CI, 1.4–26.1) and IMiDs (HR=7.9, 95%CI, 0.9–68.5) were associated with increased melanoma risk.

Conclusions: The 10y cumulative incidence of severe/life-threatening CHCs approaches 60% in long-term survivors of MM; solid SNs constitute a large burden of the morbidity. This study provides evidence for close monitoring of the survivors to manage morbidity.

Precis for use in the Table of Contents:

Cumulative incidence of grade 3–4 toxicities in multiple myeloma autologous transplant survivors approached 60% at 10 years

Cumulative incidence of subsequent neoplasms in multiple myeloma autologous transplant survivors was 13.9%±2.5%

Keywords

Hematopoietic stem cell transplant; multiple myeloma; autografts; second neoplasms; long-term survivors

Introduction

Autologous blood or marrow transplantation (aBMT), either after initial treatment or as salvage for relapsed/refractory disease is accepted as standard-of-care for multiple myeloma (MM). [1] Over past two decades, advances in therapeutic strategies for MM have led to significant improvement in overall and progression-free survival (PFS), [2] necessitating evaluation of the health and well-being of these survivors. A few studies have described PFS[3–6], and subsequent neoplasms post aBMT[7–11] in MM patients, but these have been limited by smaller sample sizes or brief post-aBMT follow-up. aBMT remains the cornerstone treatment for patients with MM, leading to higher complete response rates (59% vs. 48%) and improved PFS (median PFS 50 vs. 36 mo.). [12] MM is the most common indication for aBMT, almost 9,000 patients with MM underwent aBMT in the US in 2018. [13] With the growing number of patients living several years after a diagnosis of MM, there is a need to evaluate the health and well-being of these survivors, in order to develop evidence for risk-based anticipatory care. Using the BMT Survivor Study (BMTSS), we examined the overall burden of morbidity and the burden of subsequent neoplasms reported by MM patients who were alive two or more years from aBMT.

Methods

Bone Marrow Transplant Survivor Study (BMTSS) is a collaborative effort between University of Alabama at Birmingham, City of Hope, and University of Minnesota, examining the long-term outcomes of individuals who have survived 2 or more years after aBMT performed at the participating institutions. The Human Subjects Committee at the participating institutions approved the study; informed consent was provided according to the Declaration of Helsinki. For this report, patients were eligible if they had undergone an aBMT for MM between 1974 and 2014, had survived for 2 or more years after aBMT, and were ≥18 years of age and alive at study participation. Of the 1,171 eligible patients,

55 (4.7%) were lost to follow-up. Among the 1116 patients approached, 630 (56.5%) participated. Participants were more likely than non-participants to be white (72% *vs.* 54.3%), were older at aBMT (mean age: 57.7 *vs.* 56.2 years, p=0.007), and less likely to have undergone aBMT in recent years (median year of aBMT: 2009 *vs.* 2012, p <0.0001). Participating aBMT survivors identified a nearest-age sibling to constitute an unaffected comparison group. Siblings provide the ability to make direct comparisons with survivors and provide data on outcomes in a non-cancer population not available from other sources (vital statistics, NHIS etc.) and serve as an additional group for consistency of findings between data sources. [14,15] Siblings in the BMTSS[16–18] and another large childhood cancer survivor study (CCSS) [19] cohort have served as an effective comparison group, associated with high participation rates, ease of access, and uniformity of socio-economic status and health awareness.

The 630 MM survivors and the 289 unaffected siblings completed a 255-item BMTSS survey that included questions regarding sociodemographic characteristics (race/ethnicity, education, marital status, employment, household income, and insurance status), diagnosis by a healthcare provider of specific chronic health conditions (CHCs) along with the age at onset of CHCs. We used the common terminology criteria for adverse events (CTCAE version 5.0) to assign a level of severity to each CHC type in both the survivors and siblings. CTCAE have been used to grade health conditions in cancer survivors[18] and distinguish grades 1 through 4 for each event (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, life-threatening/disabling). Details related to MM, pre-aBMT treatment, priming for stem cell mobilization, conditioning therapy, and post-aBMT treatment were obtained from each center's BMT database, supplemented by medical record abstraction.

Statistical Analysis

Descriptive statistics were used to characterize the study population and compare between groups with χ^2 tests, exact tests, and t-tests as appropriate. The prevalence of severe (grade 3) or life-threatening (grade 4) CHCs was determined for participating aBMT survivors and siblings. The cumulative incidence of grades 3 or 4 CHCs was calculated among aBMT recipients.

Risk of CHCs in aBMT survivors compared with siblings—The magnitude of risk of any grades 3 or 4 CHCs in aBMT survivors when compared with siblings was determined using logistic regression techniques. The model was adjusted for sex, age at study participation (≥60 years *vs.* <60 years), race/ethnicity (non-Hispanic whites *vs.* others), education (<high-school, high school/some college, college graduate/post-graduate), annual household income (<$50,000, $50,000-$100,000, >$100,000), and health insurance status (yes *vs.* no). Odds ratios (ORs) with 95% confidence intervals (95%CIs) were reported.

Risk factors associated with CHCs in aBMT survivors—Cox regression analysis techniques were used to determine the factors associated with CHCs in aBMT survivors; the magnitude of association was reported as relative risk (RR) and 95%CI. Explanatory variables were selected *a priori* and were used to assess their simultaneous impact on

the risk of CHCs. These variables included age at aBMT (≥60 years *vs.* <60 years), sex, race/ethnicity (non-Hispanic whites *vs.* others), education (<high-school, high school/some college, college graduate/post-graduate), health insurance coverage (yes *vs.* no), annual household income (<$50,000, $50,000-$100,000, >$100,000), therapeutic exposures used prior to aBMT [cyclophosphamide (yes/no); vincristine, doxorubicin and dexamethasone (VAD) (yes/no); immunomodulatory drugs (IMiDs: thalidomide, lenalidomide) (yes/no); melphalan (yes/no); and radiation (yes/no)], conditioning (total body irradiation [TBI] with or without melphalan; melphalan alone; others), and transplanting institution.

Risk of subsequent neoplasms—We also examined the risk of subsequent neoplasms in the MM cohort. Using the analytic approaches described above, we calculated the cumulative incidence of all subsequent neoplasms taken together, as well as for individual types of the more prevalent subsequent neoplasms. Using Cox regression analytic methods, we examined the demographic factors and therapeutic exposures associated with an increased risk of subsequent neoplasms.

Results

Demographics and clinical characteristics of study participants

The demographic characteristics of aBMT survivors and siblings are presented in Table 1. Mean age at study participation (64.2 years *vs.* 64.0 years, p=0.7), sex (female: 42.1% *vs.* 42.2%, p=0.9) and health insurance coverage (99.2% *vs.* 99.7%, p=0.4) were comparable between aBMT survivors and siblings. Siblings were more likely to be non-Hispanic white (84.4% *vs.* 62.2% p<0.001), college graduates (56.4% *vs.* 43.8%, p<0.0001), and more likely to have an annual household income >$100,000 (41.5% *vs.* 23.5%, p<0.001) (Table 1).

Disease and transplant characteristics of the aBMT survivors are also presented in Table 1. Mean age (±SD) at aBMT was 57.6 years (±8.5), and mean interval (±SD) between aBMT and study participation was 6.6 years (±3.7). Pre-aBMT exposures included IMiDs in 63.8%, radiation in 23.2%, VAD in 17%, cyclophosphamide in 15.1% and melphalan in 4.8% of the study participants. aBMT conditioning included melphalan in 98.3% of the participants and TBI in 5.5% of the study participants (Table 1).

Burden of morbidity in aBMT survivors vs. siblings

As shown in Table 2, the prevalence of any grades 3 or 4 CHCs among aBMT survivors was 43.3%. Specific grade 3 or 4 CHCs are also detailed in Table 2. The prevalence of cataract (17.6% vs, 8.6%, p=0.0003), venous thrombo-embolism (8.1% vs 4.2%, p=0.04) and subsequent neoplasms (6.7% vs. 2.1%, p=0.004) were noted to be higher in aBMT survivors vs. siblings. In an analysis adjusted for age at questionnaire, sex, race/ethnicity, education, annual household income, and current insurance status, the aBMT survivors were at a 1.4-fold higher odds of developing a grade 3 or 4 CHC as compared to siblings (95%CI: 1.0–1.9, p=0.03).

Burden of morbidity in aBMT survivors

The 10-year cumulative incidence of any grade 3 or 4 CHC in aBMT survivors was 57.6% ±3.2% (Figure 1A). Multivariable regression analyses identified that patients with older age at BMT (≥60 years) had a 2.2-fold (95%CI: 1.7–2.9, p <0.0001) higher risk of any subsequent grade 3 or 4 CHC (Table 3), when compared to the younger patients. Those receiving a TBI-based conditioning regimen showed a trend towards a higher risk for any subsequent grade 3 or 4 CHC when compared to those not receiving TBI (RR=1.6, 95%CI: 0.95–2.7, p=0.08) (Table 3).

Subsequent neoplasms

Forty-two aBMT survivors developed 52 subsequent neoplasms. These included solid tumors (n=50), acute lymphocytic leukemia (ALL, n=1) and myelodysplastic syndrome (MDS, n=1). The solid tumors included melanoma (n=11), squamous cell cancer of the skin (n=11), basal cell carcinoma (n=6), breast cancer (n=6), prostate cancer (n=6), thyroid cancer (n=4), and 6 other miscellaneous subsequent neoplasms. The 10-year cumulative incidence of subsequent neoplasms was 13.9%±2.5% (Figure 1B). Older age at aBMT (≥60y: HR=2.1; 95%CI, 1.1–4.0, p=0.02), non-Hispanic white race/ethnicity (HR=2.4; 95%CI, 1.1–5.2, p=0.03), and pre-aBMT exposure to cyclophosphamide (HR=3.4, 95%CI,1.4–7.8, p=0.005) and IMiDs (HR=3.9, 95%CI, 1.5–9.9, p=0.005) were associated with an increased risk of subsequent neoplasms (Table 3). aBMT survivors with pre-aBMT exposure to IMiDs had a significantly higher cumulative incidence of any subsequent neoplasms when compared with those not exposed to IMiDs (19.3%±5.4% *vs.* 5.6%±2.4., p=0.007, Figure 2A).

We also evaluated risk factors associated with development of solid tumors, melanoma, and squamous cell carcinoma. The cumulative incidence of developing a solid tumor was 13.6±2.5% at 10 years (Figure 1C). aBMT survivors with pre-aBMT exposure to IMiDs had a significantly higher 10-year cumulative incidence of solid tumors when compared with those without pre-aBMT IMiD exposure (19%±5.4% *vs.* 5.6%±2.4%, p=0.009) (Figure 2B). Multivariable regression analysis (Table 3) revealed that non-Hispanic white race/ethnicity (HR=2.2; 95%CI, 1.0–4.9, p=0.04) and pre-aBMT exposure to cyclophosphamide (HR=3.5, 95%CI, 1.5–8.1, p=0.004) and IMiDs (HR=3.9, 95%CI, 1.5–10.1, p=0.005) were associated with an increased risk of solid tumors. A trend towards a higher risk of solid tumors was also seen with older age at aBMT (≥60y: HR=1.9; 95%CI, 1.0–3.6, p=0.05) (Table 3).

The cumulative incidence of developing a melanoma was 3.3%±1.2% at 10 years (Figure 1D). Pre-aBMT exposure to cyclophosphamide (HR=6.0, 95%CI, 1.4–26.0, p=0.02) was associated with a higher risk of melanoma. Pre-aBMT exposure to IMiDs (HR=7.9, 95%CI, 1.0–68.5, p=0.06) showed a trend towards a higher risk of melanoma (Table 3, Figure 2C). The cumulative incidence of developing a SCC was 5.1%±1.8% at 10 years (Figure 1E). Older age at BMT (≥60 years) was associated with a trend towards a higher risk of SCC (HR=3.1, 95%CI,0.9–10.6, p=0.07) (Table 3). Prior IMiD exposure did not impact risk of SCC (Figure 2D, Table 3).

Discussion

We found a significant burden of morbidity borne by MM survivors, such that the cumulative incidence of severe/life-threatening CHCs approached 60% at 10 years after aBMT. This represented a 40% higher burden of severe/life threatening morbidity when compared with siblings. In particular, we found that the 10-year cumulative incidence of solid subsequent neoplasms among those exposed to IMiDs approached 20%.

The 5-year cumulative incidence of any severe/life-threatening CHCs was 37.5% and increased to 57.6% by 10 years from aBMT in this cohort of MM patients treated with aBMT and followed for an average of 6.6 years. The incidence continues to climb, with no evidence of a plateau. We found older age at aBMT (≥60 years) and TBI-based conditioning to be associated with a higher burden of grades 3–4 toxicities, thus identifying vulnerable populations that need close long-term follow-up. The most prevalent morbidities were subsequent neoplasms, venous thrombo-embolism, and cataracts. Venous thrombo-embolism is reported to occur at a higher frequency in patients with MM. [27] Cataracts are a well-described complication after BMT, and similar to prior studies evaluating aBMT survivors of lymphoma[24,26], we noted a higher frequency of cataracts in long term survivors of aBMT for MM. However, the burden of morbidity due to other grade 3–4 CHCs was comparable between the survivors and the sibling comparison group, with the exception of coronary artery disease and thyroid dysfunction (lower in survivors). This was likely due to the older age of both the survivors and siblings, contributing to the presence of comorbidities in both groups. Nonetheless, this study provides us with an opportunity to provide risk-based surveillance.

Previous studies have suggested an increased risk of subsequent neoplasms in patients with MM; [7,9,10,28,29] ranging between 3% and 20%[28], depending on the methodology for ascertainment of subsequent neoplasms, and the length of follow-up (≤5 years in most studies[9,10,29]). Studies have reported exposure to alkylating agents, lenalidomide, melphalan, TBI, and older age at exposure to be associated with subsequent neoplasms. [28] In our cohort, we found the cumulative incidence of subsequent neoplasms to approach 14% at 10 years post-aBMT. We identified older age, non-Hispanic white race/ethnicity, and pre-aBMT exposure to cyclophosphamide and IMiDs to be associated with a higher risk of subsequent neoplasms. We found a higher risk of subsequent neoplasms in non-Hispanic whites as compared to other groups. This may be in part due to the higher number of skin cancers in our study. A previous SEER-based analysis also demonstrated an increased risk of developing melanomas, non-Hodgkin lymphoma, and acute myeloid leukemia in non-Hispanic whites[28,30], when compared with the general population.

Unlike previous studies, solid tumors constituted 96% of subsequent neoplasms in our study; among the solid tumors, melanoma and squamous cell carcinoma of the skin were the most prevalent. When evaluating risk factors for development of these tumors, older age at aBMT, non-Hispanic white race and ethnicity and prior exposure to cyclophosphamide and IMiDs were associated with higher risk of solid tumors overall, and especially of melanomas. The pathogenesis of subsequent neoplasms among MM patients is not well understood. Genetic factors[31], interacting with therapeutic exposures, especially with

immune-modulating agents[32], could play a role and need to be examined in detail. A large analysis from CIBMTR found a higher incidence of acute myeloid leukemia and melanoma after autologous transplant for MM[11]. A similar increase has been reported in other transplant settings and in persons with immunesuppression[33]. Prior studies including a large meta-analysis evaluated development of subsequent neoplasms in patients exposed to lenalidomide and found a higher incidence of hematologic malignancies. [29] In our study, two patients developed hematologic malignancies, 1 each with ALL and MDS. Our study also demonstrated an association of solid malignancies with cyclophosphamide. Studies have reported an association of leukemia[34], bladder cancer[35], and bone cancer[36] with higher cumulative doses of cyclophosphamide. Pathogenetic mechanisms postulated include DNA double-strand break-induced gene translocations and genomic instability due to loss of DNA repair[37–39]. The presence of inherited genetic polymorphisms may also modulate the risks of solid cancers after alkylator-based chemotherapy[40].

Our results differ from prior studies[29] perhaps due to differences in the study population. Inclusion of ≥2 year survivors in our cohort could possibly result in an under-estimation of MDS because of the short latency accompanied by the high fatality rate. Further, our study had longer follow-up, allowing for emergence of solid tumors with longer latency.

We acknowledge the limitations in our study, particularly the lack of information regarding dose and duration of IMiD exposure, the lack of information regarding post-aBMT therapeutic exposures, and reliance on self-report. The reliability and validity of the BMTSS questionnaire have been tested, and the responses have demonstrated a high level of sensitivity and specificity, [41] confirming that survivors are able to report the occurrence of adverse medical conditions with accuracy. Further, the subsequent neoplasms in our study were confirmed with pathology reports and/or clinician reports. These limitations notwithstanding, in this large cohort of MM patients followed long-term, this study describes the overall burden of severe/life-threatening morbidity, with emphasis on the risk of subsequent neoplasms after exposure to therapeutic agents.

In conclusion, the burden of severe/life-threatening CHCs approaches 60% in MM patients treated with aBMT. Subsequent neoplasms constitute a significant burden of morbidity. This study identifies demographic factors and treatment exposures associated with increased risk of CHCs and subsequent neoplasms, and provides evidence for close monitoring of these survivors to anticipate and manage morbidity.

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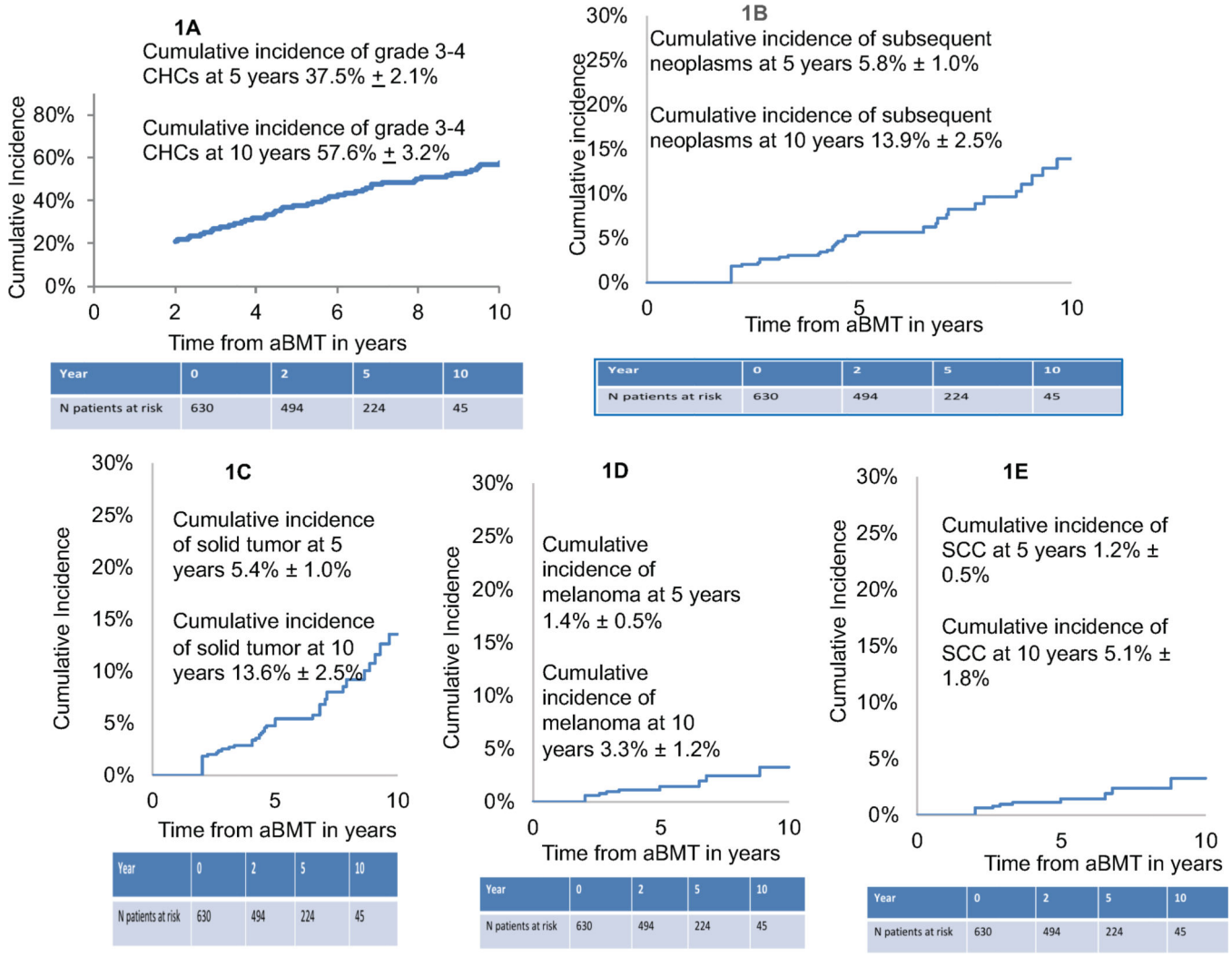


Figure 1.

Figure 1A: Cumulative incidence of any grade 3–4 Chronic Health Condition in aBMT survivors

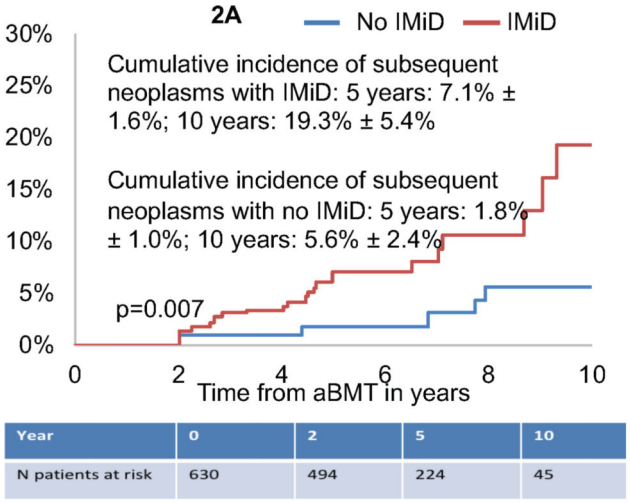
Figure 1B: Cumulative incidence of any subsequent malignant neoplasms in aBMT survivors

Figure 1C: Cumulative incidence of Solid Tumors in aBMT survivors

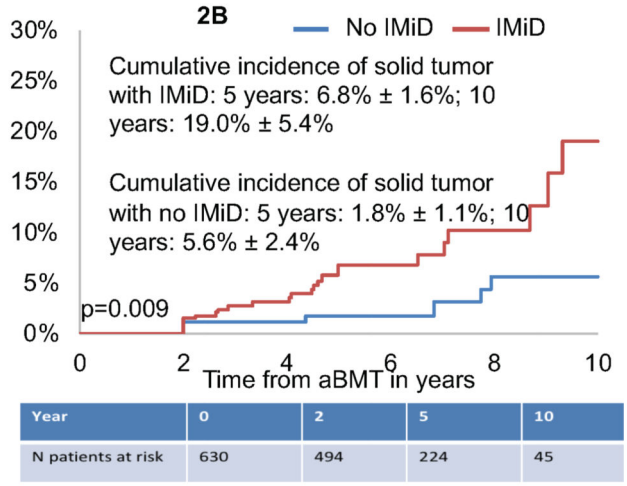
Figure 1D: Cumulative incidence of Melanoma in aBMT survivors

Figure 1E: Cumulative incidence of SCC in aBMT survivors

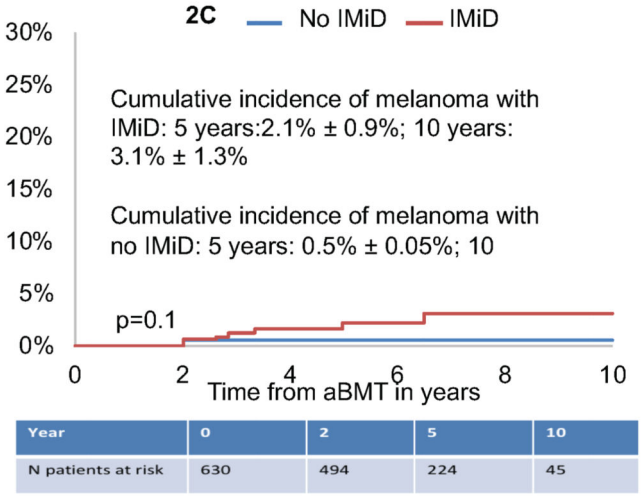
Abbreviations: aBMT: Autologous blood or marrow transplantation, SCC: squamous cell carcinoma, CHC: chronic health condition



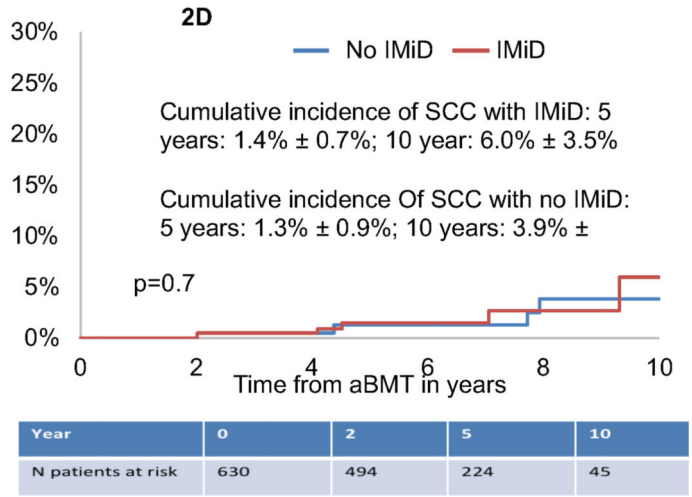
Year	0	2	5	10
N patients at risk	630	494	224	45



Year	0	2	5	10
N patients at risk	630	494	224	45



Year	0	2	5	10
N patients at risk	630	494	224	45



Year	0	2	5	10
N patients at risk	630	494	224	45

Figure 2.

Figure 2A: Cumulative incidence of any subsequent malignant neoplasms in aBMT survivors by IMiD exposure

Figure 2B: Cumulative incidence of Solid Tumors in aBMT survivors by IMiD exposure

Figure 2C: Cumulative incidence of Melanoma in aBMT survivors by IMiD exposure

Figure 2D: Cumulative incidence of SCC in aBMT survivors by IMiD exposure

Abbreviations: aBMT: Autologous blood or marrow transplantation, SCC: squamous cell carcinoma, IMiD: Immunomodulatory drugs

Table 1:

Demographic and Clinical Characteristics of the Study Participants

Characteristics	Survivor (n=630)	Sibling (n=289)	P-value
Age at aBMT (years, mean ± SD)	57.6 ± 8.5	NA	
Interval between aBMT and survey (mean, years± SD)	6.6 ± 3.7	NA	
Age at survey (mean, years± SD)	64.2 ± 7.9	64.0 ± 8.1	0.7
Sex n (%)			
Female	265 (42.1)	122 (42.2)	1.0
Race and Ethnicity n (%)			
White	393 (62.2)	244 (84.4)	<0.001
Hispanic	109 (17.3)	18 (6.2)	
Black	87 (13.8)	9 (3.1)	
Asian	21 (3.3)	14 (4.8)	
Mixed/other/unknown	21 (3.3)	4 (1.4)	
Education n (%)			
<High school	42 (6.7)	5 (1.7)	0.0001
High school and some college	311 (49.4)	121 (41.9)	
College graduate and post-graduate	276 (43.8)	163 (56.4)	
Missing	1 (0.16)	0 (0.00)	
Annual household income n (%)			
< $50,000	188 (29.8)	49 (16.7)	<0.001
$50,000-$100,000	205 (32.5)	89 (30.8)	
>$100,000	148 (23.5)	120 (41.5)	
Missing	89 (14.1)	31 (10.7)	
Current insurance n (%)			
Yes	625 (99.2)	288 (99.7)	0.4
Conditioning n (%)			
Cyclophosphamide	40 (7.60)	NA	
Melphalan	517 (98.3)	NA	
TBI	29 (5.5)	NA	
Other	38 (7.2)	NA	
Missing	104	NA	
Therapeutic exposures pre-aBMT n (%)			
Cyclophosphamide	78 (15.1)	NA	
Melphalan	25 (4.8)	NA	
Steroids	512 (99)	NA	
Doxorubicin	113 (21.9)	NA	
Bortezomib	270 (52.2)	NA	
Vincristine	93 (18)	NA	
IMiD (Thalidomide or lenalidomide)	330 (63.8)	NA	

Characteristics	Survivor (n=630)	Sibling (n=289)	P-value
Radiation therapy	120 (23.2)	NA	
Other	20 (3.9)	NA	
Missing	113	NA	
Grade 3–4 Chronic Health Conditions			
Yes	273 (43.3)	107 (37)	0.07

Abbreviations: TBI: total body radiation, IMiD: Immunomodulatory drugs

Table 2:

Prevalence of Grade 3–4 Chronic Health Conditions in aBMT Survivors and Siblings

Chronic Health Conditions	Survivor n (%)	Sibling n (%)	P-value
Any grades 3–4 CHC	273 (43.3%)	107 (37.0%)	0.07
Auditory			
Hearing loss	38 (6.0%)	27 (9.3%)	0.07
Ocular			
Legally blind	5 (0.8%)	5 (1.7%)	0.3
Cataract	111 (17.6%)	25 (8.7%)	0.0003
Renal			
Renal failure requiring dialysis	0 (0%)	1 (0.4%)	0.3
Endocrine			
Thyroid dysfunction	6 (1%)	9 (3.1%)	0.02
Diabetes mellitus	12 (1.9%)	8 (2.8%)	0.5
Musculoskeletal			
Joint replacement	33 (5.2%)	25 (8.7%)	0.06
Cardiovascular disease			
Coronary artery disease	22 (3.5%)	19 (6.6%)	0.04
Congestive heart failure	10 (1.6%)	6 (2.1%)	0.6
Arrhythmia	11 (1.8%)	3 (1.0%)	0.6
Valvular heart disease	1 (0.2%)	1 (0.4%)	0.5
Cerebrovascular disease	14 (2.2%)	8 (2.8%)	0.6
Venous thrombo-embolism	51 (8.1%)	12 (4.2%)	0.03
Pulmonary disease			
Any pulmonary condition	5 (0.8%)	0 (0%)	0.3
Gastrointestinal disease			
Liver disease	2 (0.3%)	1 (0.4%)	1.0
Gastro-intestinal disease	7 (1.1%)	1 (0.4%)	1.0
Neurological disease			
Any neurological condition	5 (0.8%)	3 (1.0%)	0.7
Subsequent neoplasms	42 (6.7%)	6 (2.1%)	0.004

Table 3:

Cox Regression Analysis of Specific Chronic Health Conditions in Multiple Myeloma Patients Treated with aBMT

Variable	Any grades 3–4 CHC		Subsequent neoplasms		Solid tumor		Melanoma		SCC	
	HR (95%CI)	p-value	HR (95% CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age at aBMT (referent group <60y)										
Age at aBMT ≥60y	2.24 (1.7–2.9)	<0.0001	2.12(1.12–4.01)	0.02	1.90(1.0–3.6)	0.05			3.07(0.9–10.6)	0.08
Race/ethnicity (referent group: non-white)										
Non-Hispanic white	1.26 (0.98–1.6)	0.08	2.38(1.1–5.17)	0.03	2.23(1.0–4.9)	0.04				
Conditioning										
TBI ± other	1.59 (0.95–2.7)	0.08								
Pre-aBMT therapeutic exposures										
Cyclophosphamide			3.36(1.44–7.84)	0.005	3.46(1.5–8.1)	0.004	6.02(1.4–26.1)	0.02		
IMiD			3.86(1.49–9.94)	0.005	3.89(1.5–10.1)	0.005	7.9(0.9–68.5)	0.06		

Abbreviations: aBMT: Autologous hematopoietic cell transplant, HR: hazard ratio, CI: confidence interval, IMiD: Immunomodulatory drug (Thalidomide or Lenalidomide), TBI: total body irradiation, SCC: squamous cell carcinoma