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Association between Clonal Hematopoiesis and Late Nonrelapse Mortality after Autologous Hematopoietic Cell Transplantation

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Abstract

Clonal hematopoiesis (CH), characterized by the accumulation of acquired somatic mutations in the blood, is associated with an elevated risk of aging-related diseases and premature mortality in non-cancer populations. Patients who undergo autologous hematopoietic cell transplantation (HCT) are also at high risk of premature onset of aging-related conditions. Therefore, we examined the association between pretreatment CH and late-occurring (≥1 year) nonrelapse mortality (NRM) after HCT. We evaluated pathogenic and likely pathogenic CH variants (PVs) in 10 patients who developed NRM after HCT and in 29 HCT recipient controls matched by age at HCT ± 2 years (median, 64.6 years; range, 38.5 to 74.7 years), sex (79.5% male), diagnosis (61.5% with non-Hodgkin lymphoma, 18.0% with Hodgkin lymphoma, and 20.5% with multiple myeloma), and duration of follow-up. We analyzed mobilized hematopoietic stem cell DNA in samples collected before HCT using a custom panel of amplicons covering the coding exons of 79 myeloid-related genes associated with CH. PVs with allele fractions >2% were used for analyses. Cases were significantly more likely than controls to have CH (70% versus 24.1%; $P = .002$), to have ≥2 unique PVs (60% versus 6.9%; $P < .001$), and to have PVs with allelic fractions ≥10% (40% versus 3.4%; $P = .003$). Here we provide preliminary evidence of an association between pre-HCT CH and NRM after HCT independent of chronologic age. Integration of CH analyses may improve the accuracy of existing pre-HCT risk prediction models, setting the stage for

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personalized risk assessment strategies and targeted treatments to optimally prevent or manage late complications associated with HCT.

Keywords

Lymphoma; Multiple myeloma; Nonrelapse mortality; Autologous; Transplantation; Clonal hematopoiesis; Survivors

INTRODUCTION

Despite improvements in long-term outcomes, autologous hematopoietic cell transplantation (HCT) survivors continue to have substantially higher mortality rates than the general population [1–3]. In particular, their risk of nonrelapse mortality (NRM; eg, subsequent neoplasms [SNs], cardiovascular disease [CVD], respiratory failure) is more than double that of the general population [2,4]. Moreover, long-term HCT survivors have a 4- to 6-fold greater risk of developing SNs and CVD compared with the general population, and the magnitude of risk for these complications and others increases over time after HCT [1,5–7].

Several aging-related diseases also develop earlier in HCT survivors than would be expected in the general population. For example, among HCT survivors, the median age at first cardiovascular event, such as myocardial infarction, is 53 years (range, 35 to 66 years), which is much younger than the median age in the general population (67 years). The substantially greater risk of health-related complications, coupled with the development of diseases earlier than would be expected in the general population, suggests an accelerated aging phenotype in HCT survivors [8,9]. However, there is marked variability in the aging phenotype in this population that is not explained exclusively by clinical risk factors (eg, patient age, sex, chronic health conditions) or treatment exposures (eg, cytotoxic chemotherapy, radiation therapy) alone [8,10].

Population studies suggest that age-associated diseases, such as acute myelogenous leukemia and CVD, are influenced by the interaction between canonical genetic drivers of hematologic malignancies (eg, clonal hematopoiesis [CH] involving myeloid genes) and the cumulative effects of key genotoxic exposures (eg, smoking, or chemotherapy/radiation) during an individual's lifetime [11–14]. In a recent cohort study of patients with lymphoma who underwent autologous HCT for relapsed/refractory disease (median age, 58 years), the prevalence of pre-HCT CH was 29.9% [15], which is comparable to that observed in non-cancer patients in their tenth decade of life [12]. The high rate of pre-HCT CH was thought to be due in part to previous chemotherapy exposure (median number of pre-HCT treatment regimens, 2; range, 1 to 6) and was associated with a higher incidence of hematologic malignancies, including therapy-related myelodysplastic syndrome and acute myelogenous leukemia, which contributed significantly to the elevated NRM in this cohort. Other aging-related complications, such as CVD, also may have contributed to the high NRM [15]; however, the proportion of elderly patients (age ≥60 years at HCT) was much higher among patients with CH compared with those without CH (58.3% versus 35.6%; $P < .001$) [15]. Accordingly, we evaluated the prevalence of pre-HCT CH in patients who developed late-occurring (≥1 year after HCT) NRM after autologous HCT (cases) and matched controls,

defined as alive at last follow-up or died due to relapse after a comparable survival period. We hypothesized that cases would be more likely than controls to have any pathogenic and likely pathogenic CH variants (PVs), as well as multiple (≥2) PVs, before HCT.

METHODS

Study Participants

We identified 10 patients who developed NRM (SN, CVD, or organ failure) ≥1 year after autologous HCT performed at City of Hope (COH; cases) for lymphoma or multiple myeloma between 2012 and 2014. Cases were matched 1:3 with 29 controls on age at HCT ±2 years, sex, diagnosis, and duration of follow-up after HCT. Both cases and controls had to have stored hematopoietic stem cells available for analysis. This study was approved by the COH Institutional Review Board (IRB #18076), and informed consent was waived owing to the study's retrospective nature.

CH Genomic Analysis

We evaluated mobilized peripheral blood hematopoietic stem cell DNA in samples collected before HCT. DNA was extracted using the DNEasy Blood and Tissue Kit (QIAGEN, Redwood City, CA). All samples yielded high-quality DNA (A_{260}/A_{280} ratio >1.7). Genomic libraries were prepared at the COH Integrative Genomics Core using a custom QIAGEN QIAseq panel of amplicons covering the coding exons of 79 myeloid-related genes associated with CH. The panel evaluated the coding exons ±10 base pairs into the introns of the following known and candidate CH-related-genes: *AKT1, ANKRD26, ARID1A, ASXL1, ATM, BCORL1, BIRC3, BRAF, CBL, CCND1, CCND3, CDKN2A, CEBPA, CHEK2, CREBBP, CTC1, DAXX, DDX41, DKC1, DLC1, DNMT3A, EP300, ETV6, EZH2, FBXW7, FLT3, GATA2, GNAS, GNB1, HAX1, HRAS, IDH1, IDH2, IRF1, JAK2, KIT, KMT2D, KRAS, MPL, MYC, MYD88, NF1, NHP2, NOP10, NPM1, NRAS, NXF1, PAX5, PHF6, PHIP, PIK3CA, PPM1D, PTEN, PTPN11, RET, RPS19, RUNX1, SETBP1, SF3B1, SMAD4, SRCAP, SRP72, SRSF2, STAG2, STAT3, STX11, TERC, TET2, TINF2, TP53, TRAF3, TRRAP, U2AF1, UBR5, WT1, YLPM1, ZBTB33, ZNF318, and ZRSR2*.

Prepared libraries were sequenced on an Illumina HiSeq 2500 in the Integrative Genomics Core using 100 paired-end reads. Variants were annotated using Ingenuity Variant Analysis version 5.3.20180727 (QIAGEN), with manual review by an expert board-certified in molecular diagnostics (T.P.S.). PVs and likely PVs [16] with allele fractions >2% at loci with read depths of at least 5 reads were used for analyses.

Statistical Considerations

Descriptive statistics were generated for all outcome measures. Exploratory analyses were performed to describe the associations between participant demographics, chronic health conditions, and CH. Conditional logistic regression for 1:3 matching was used for comparisons between groups; a P value <.05 was considered statistically significant. Data were analyzed using SPSS version 24 (IBM, Armonk, NY).

RESULTS

Patient characteristics are summarized in Table 1. Because of matching, there were no differences in age at HCT, sex, or diagnoses between cases and controls. The median age at HCT was 64 years (range, 38 to 74 years), 79.5% of the patients were male, and 61.5% underwent HCT for non-Hodgkin lymphoma, 18.0% for Hodgkin lymphoma, and 20.5% for multiple myeloma (Table 1). Among the cases, median time from HCT to NRM was 2.0 years (range, 1.1 and 3.9 years), and causes of death were SN in 60%, multiorgan failure in 20%, CVD in 10%, and respiratory failure in 10% (Table 1).

The average read depth postsequencing was 560×; 1395 of 1398 sequencing targets (99.8%) were covered with a read depth >100×. The overall prevalence of CH was 35.9%. Cases were significantly more likely than controls to have CH (70% versus 24.1%; P = .002). Cases were also significantly more likely to have multiple (≥2) unique PVs (60% versus 6.9%; $P < .001$) and to have PVs with high (≥10%) allelic fractions (40% versus 3.4%; $P = .003$) (Table 2).

A complete list of PVs identified in all patients is provided in Table 2. PVs were found most commonly in *PPM1D*, with 9 mutations in 5 patients, followed by *DNMT3A* (6 mutations in 5 patients), *TET2* (4 mutations in 4 patients), and *TP53* and *SRCAP* (each with 3 mutations in 3 patients). Two cases with CH developed therapy-related myelodysplastic syndrome, both of whom had PVs in *PPM1D*. Cases with respiratory and multiorgan failure had PVs in *TET2*. Seventeen unique PVs had not yet been reported in the Catalogue of Somatic Mutations in Cancer (COSMIC; https://cancer.sanger.ac.uk/cosmic) database (Table 2). Moreover, 11 of these 17 were apparently novel with no variant literature according to Ingenuity Variant Analysis.

The variant allele fractions ranged from 2.1% to 46.7%. The majority of variants had allele fractions well under 30% and thus are unlikely to represent germline variant contamination. The 3 variants with allele fractions >30% were in *TET2* (×2) and *PPM1D*. Although these may be indicative of germline mutations, *TET2* and *PPM1D* germline mutations are rare. Variants in these genes are known to be common drivers of CH, which can be represented by higher variant allele fractions, likely explaining the higher allele fractions reported herein [17–19].

DISCUSSION

Our pilot study provides preliminary evidence to clarify and support an apparent association between preautologous HCT CH and NRM outcomes after HCT, irrespective of chronological age. Consistent with our hypothesis, we identified that patients who died of non-relapse-related causes following autologous HCT were more likely to have CH at the time of transplantation. The overall prevalence (35.9%) of pre-HCT CH was similar to the 29.9% reported by Gibson et al [15] in the study that originally suggested the association in patients undergoing autologous HCT for lymphoma. Of note, our cases and controls included patients undergoing autologous HCT for multiple myeloma as well as for lymphoma. In these patients, we found that late-occurring NRM was frequently associated

with the presence of more than 1 PV, as well as PVs with higher allele fractions. The latter finding is noteworthy because PVs with higher allele fractions have previously been associated with an elevated risk for developing hematologic disease in the noncancer population [12].

Many PVs in our study, particularly those in *PPM1D*, had not been previously reported in the literature, whereas others were not seen previously in the COSMIC database—one of the largest databases for somatically acquired mutations identified in human cancer. Of note, *PPM1D* (mutated in 3 cases and 2 controls), *TP53* (mutated in 3 cases), and *SRCAP* (mutated in 2 cases and 1 control) have been associated with the DNA damage response pathway, and their PVs are significantly more prevalent in patients exposed to cytotoxic therapy [17], which was the case for all of the patients in this cohort. Interestingly, Gibson et al [15], in the other main study on this topic, also identified a *PPM1D* p.A481fs mutation; however, this was the result of a different complementary DNA change, c.1441delG, than the complementary DNA change identified in our study, c.1440_1453delAGCCCTGACTTTAA (Table 2). Therefore, this amino acid position may be an important hotspot region for CH mutations in the pre-HCT patient population.

We acknowledge that because of our limited sample size, we are not able to comment on the causal implications of individual PVs and different causes of NRM. However, it is well recognized that CH likely increases NRM at least through an increased risk of secondary malignancies and cardiovascular disease; other associations are less clear but certainly possible given the general proinflammatory nature of CH. Although in any given patient, it may be difficult to separate the relative contributions of the genotoxic stress of cytotoxic chemotherapy versus aging-related clonal hematopoiesis, certain mutations do appear to be more associated with the former (eg, *PP1MD*). Additional studies are needed to understand the dynamics of clonal evolution and the relative allele fractions of particular mutations with specific adverse outcomes after cancer treatment.

Although the somatic mutations identified in our study may represent circulating tumor DNA rather than true CH, we all patients underwent HCT with a low overall burden of disease; to be candidates for HCT, the patients with non-Hodgkin lymphoma and Hodgkin lymphoma could not have had overt bone marrow involvement. Second, the majority of the mutations identified are much more likely to be associated with CH than with a malignant clone. For instance, *DNMT3A* mutations have been described in myeloid malignancies (frequently) and in T cell lymphomas (less often) but are not known to be recurrently mutated in B cell lymphomas [20]. Similarly, somatic mutations in *PPM1D* have been identified as drivers of CH, especially in the context of previous cytotoxic chemotherapy [11,17], but have been described in only a few cases of mantle cell lymphoma.

The primary limitation of this study was its small sample size, which limited our ability to perform detailed analyses regarding pre-HCT therapeutic exposures and CH, as well as to examine outcomes other than NRM, such as severe or life-threatening health conditions that might not have resulted in NRM. Small case-control studies such as this may be prone to selection bias. Therefore, our results should be interpreted with caution. Larger studies are currently underway to evaluate the association between CH and outcomes after HCT to

develop risk prediction models that can be readily used to stratify patients before HCT. Literature is also lacking on a possible loss of correlation between CH variant identification from mobilized peripheral blood hematopoietic stem cells and that from nonmobilized peripheral white blood cells. Another limitation was that the study was not designed to compare CH variants with an allele fraction <2%, which may be meaningful in some cases. As noted in Results, some CH-related variants may have represented germline contamination, although this is unlikely. Future studies evaluating CH-related variants may need to incorporate orthogonal tissues (ie, buccal swab or skin biopsy) for evaluation. Given our relatively small sample size, we also did not evaluate as many CH-related genes as were evaluated in the main comparator study [15]; future studies could explore a broader range of genes and their variants.

The implications of this research are potentially far-reaching and could encompass changes to cancer treatment, improvements to the well-being of cancer survivors, and insights into the biology of treatment complications. Understanding the association between pre-HCT risk factors (including CH status) and subsequent late effects may one day prove critical for helping patients and their physicians in real-time decision making both before HCT (eg, consideration of longer use of checkpoint inhibitors or monoclonal antibodies as a strategy to avoid HCT in patients at greatest risk for complications) and during HCT (eg, selection of allogeneic HCT to eliminate clonal hematopoiesis of indeterminate potential in patients with diseases associated with a high risk for relapse). Furthermore, this research may also be important for informing HCT survivors and their caregivers as they consider plans for long-term surveillance and follow-up. A recent study of 81 patients undergoing autologous HCT found that CH mutations present before HCT were more likely to dominate blood reconstitution over wild-type hematopoietic stem cells after HCT [21], leading to an increased future risk of CH-associated complications in survivors. Therefore, information on CH status (either before or after HCT) may allow for implementation of more frequent screening intervals and management of modifiable risk factors in at-risk individuals.

Our findings may also contribute to the development of the next generation of therapeutics that can effectively eliminate cancer with minimal adverse side effects. For example, one potential explanation for our findings is that CH involving myeloid genes may trigger accelerated aging or inflammatory pathways [18]. In support of this hypothesis, preclinical work has shown that mice with *TET2* deficiency experience accelerated atherosclerosis [22]. Thus, future research could focus on identifying and developing strategies to block the aberrant activation of these pathways.

In conclusion, our present data provide additional insight into efforts to integrate CH analyses into existing autologous HCT risk prediction models. The incorporation of CH findings may improve the ability of these models to identify individuals at high risk for NRM, enabling the development of personalized risk assessment strategies and targeted treatments that optimally prevent or manage complications associated with autologous HCT. The development of such strategies is imperative to ensure that the growing population of long-term HCT survivors (>500,000 by 2030) [23] can live long and healthy lives well after the completion of HCT.

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Table 1

Characteristics of Study Participants (N = 39)

Characteristic	Cases (N = 10)	Controls (N = 29)	Combined (N = 39)
Age at HCT, yr, median (range)	62.6 (42.1–74.6)	64.6 (38.5–74.7)	64.6 (38.5–74.7)
Male sex, n (%)	8 (80.0)	23 (79.3)	31 (79.5)
Race/ethnicity, n (%)			
Non-Hispanic white	7 (70.0)	27 (69.0)	27 (69.2)
Hispanic	0	3 (10.3)	3 (7.7)
Other	3 (30.0)	9 (20.7)	9 (23.1)
Diagnosis, n (%)			
Non-Hodgkin lymphoma	6 (60.0)	18 (62.1)	24 (61.5)
Hodgkin lymphoma	2 (20.0)	5 (17.2)	7 (18.0)
Multiple myeloma	2 (20.0)	6 (20.7)	8 (20.5)
Conditioning regimen, n (%)			
BEAM	4 (40.0)	13 (44.8)	17 (43.5)
Zevalin + BEAM	2 (20.0)	5 (17.2)	7 (18.0)
BCNUCYVP16	2 (20.0)	5 (17.2)	7 (18.0)
Melphalan	2 (20.0)	6 (20.7)	8 (20.5)
Causes of death, N (%)			
Subsequent hematologic neoplasm	4 (40.0)	–	–
Subsequent solid neoplasm	2 (20.0)	–	–
Multi-organ failure	2 (20.0)	–	–
Cardiovascular disease	1 (10.0)	–	–
Respiratory failure	1 (10.0)	–	–

BEAM indicates carmustine, etoposide, cytarabine, and melphalan; BCNUCYVP16, carmustine, cyclophosphamide, and etoposide.

Table 2

CH Variants and NRM

ID	Number of CH Variants	Gene Variant Summary with Allele Fraction	Sex	Age at HCT, yr	Diagnosis	Cause of Death
Cases						
1	3	PPM1D (NM_003620.3,17q23.2: g.58740365, c.1270G>T, p.E424*, stop gain, 4.86%)†,‡	F	59	NHL	SN (tMDS)
		PPM1D (NM_003620.3,17q23.2: g.58740749, c.1654C>T, p.R552*, stop gain, 2.14%)				
		TP53 (NM_000546.5,17p13.1: g.7577121, c.817C>T, p.R273C, missense, 4.04%)				
2	4	DNMT3A (NM_022552.4, 2p23.3: g.25458661, c.2512A>G, p.N838D, missense, 3.66%)	M	70	NHL	SN (tMDS)
		PPM1D (NM_003620.3,17q23.2: g.58740532, c.1440_1453delAGCCCTGACTTTAA, p.A481fs*3, frameshift, 2.26%)†,‡				
		PPM1D (NM_003620.3,17q23.2: g.58740659, c.1564A>T, p.K522*, stop gain, 7.46%)†,‡				
		PPM1D (NM_003620.3,17q23.2: g.58740749, c.1654C>T, p.R552*, stop gain, 2.43%)				
3	3	PPM1D (NM_003620.3,17q23.2: g.58740695, c.1601_1602delTT, p.F534*, frameshift, 33.88%)†	M	55	HL	SN (AML)
		TET2 (NM_001127208.2,4q24: g.106158157, c.3058delC, p.Q1020fs*13, frameshift, 3.32%)				
		TP53 (NM_000546.5,17p13.1: g.7578394, c.536A>G, p.H179R, missense, 4.27%)				
4	2	PHIP (NM_017934.6,6q14.1: g.79655960, c.4387dupA, p.R1463fs*35, frameshift, 2.78%)†,‡	M	64	NHL	Multiorgan failure
		TET2 (NM_001127208.2,4q24: g.106158026, c.2927delA, p.Q976fs*31, frameshift, 43.04%)†,‡				
5	4	DNMT3A (NM_022552.4, 2p23.3: g.25469173, c.1285A>T, p.K429*, stop gain, 25.75%)	M	68	MM	Organ failure (respiratory)
		SRCAP (NM_006662.2,16p11.2: g.30744681, c.6208C>T, p.R2070*, stop gain, 2.02%)†,‡				
		TET2 (NM_001127208.2,4q24: g.106157698, c.2599T>C, p.Y867H, missense, 46.7%)				
		TP53 (NM_000546.5,17p13.1: g.7577120, c.818G>A, p.R273H, missense, 2.47%)				
6	1	SRCAP (NM_006662.2,16p11.2: g.30731534, c.2869C>T, p.R957*, stop gain, 8.85%)†,‡	M	74	NHL	Organ failure (CVD)
7	2	DNMT3A (NM_022552.4, 2p23.3: g.25458644, c.2528dupG, p.K844fs*11, frameshift, 4.03%)†,‡	M	65	NHL	Multiorgan failure
		KMT2D (NM_003482.3,12q13.12: g.49425038, c.13450C>T, p.R4484*, stop gain, 27.4%)†				

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ID	Number of CH Variants	Gene Variant Summary with Allele Fraction	Sex	Age at HCT, yr	Diagnosis	Cause of Death
8	0	N/A	M	60	MM	SN (tMDS)
9	0	N/A	F	42	HL	SN (lung cancer)
10	0	N/A	M	59	NHL	SN (prostate cancer)
Controls[§]						
1	1	TET2 (NM_001127208.2,4q24: g.106162499, c.3415delA, p.I1139fs*13, frameshift, 2.14%)	F	59	NHL	-
2	1	SRCAP (NM_006662.2,16p11.2: g.30732525, c.3269delT, p.L1090fs*4, frameshift, 5.6%)[†,‡]	M	74	NHL	-
3	1	PTEN (NM_000314.6,10q23.31: g.89720651, c.802delG, p.D268fs*8, frameshift, 7.14%)[†]	M	68	MM	-
4	2	PPM1D (NM_003620.3,17q23.2: g.58740613, c.1519_1520delGT, p.V507fs*20, frameshift, 2.26%)[†,‡]	M	72	NHL	
		PPM1D (NM_003620.3,17q23.2: g.58740542, c.1447delA, p.T483fs*2, frameshift, 5.1%)[†,‡]				
5	1	PPM1D (NM_003620.3,17q23.2: g.58740732, c.1637delT, p.L546fs*2, frameshift, 2.5%)[†]	M	60	HL	-
6	2	DNMT3A (NM_022552.4, 2p23.3: g.25464544, c.1969G>A, p.V657M, missense, 5.97%)[†]	M	69	NHL[//]	
		DNMT3A (NM_022552.4, 2p23.3: g.25470485, c.989G>A, p.W330*, stop gain, 3.46%)[†]				
7	1	DNMT3A (NM_022552.4, 2p23.3: g.25458595, c.2578T>C, p.W860R, missense, 17.12%)	M	66	NHL	-

Genomic coordinates per the hg19 release.

NHL indicates non-Hodgkin lymphoma; tMDS, therapy-related myelodysplastic syndrome; HL, Hodgkin lymphoma; AML, acute myelogenous leukemia; MM, multiple myeloma; N/A, not applicable.

[†]Not previously reported in the Catalogue of Somatic Mutations in Cancer (COSMIC) database.

[‡]Novel variant.

[§]Controls without CH are not shown.

[//]Control with persistent disease.