Leukemia Research 84 (2019) 106193

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Chronic lymphocytic leukemia patients with HLA-B27 referred for allogeneic hematopoietic stem cell transplantation do not have worse outcomes: Results of a population-based case series analysis in British Columbia, Canada

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ARTICLE INFO

Keywords:
CLL
HLA-B27
Ankylosing spondylitis
Spondyloarthritis
Outcome
Case series

ABSTRACT

Human leukocyte antigen B27 (HLA-B27), associated with spondyloarthritis, was suggested to be protective against chronic lymphocytic leukemia (CLL). It is hypothesized that HLA-B27 patients may have worse outcome in part related to their other comorbidities.

Objectives: We sought to compare the clinical characteristics and outcomes of CLL and small lymphocytic lymphoma (SLL) patients referred for allogeneic hematopoietic stem cell transplantation (allo-HSCT) based on their HLA-B27 status.

Methods: This retrospective population-based case series analyzed CLL/SLL patients who were HLA-typed for potential allo-HSCT in British Columbia, Canada.

Results: of 279 CLL/SLL patients referred for potential allo-HSCT, 34 patients were HLA-B27 positive. For HLA-B27 patients, median age at CLL diagnosis was 53.5 years (range, 27–67) and 71% were male. Seven patients had 11q deletion and nine patients had 17p deletion detected prior to first CLL therapy or at relapse. Eleven HLA-B27 patients received allo-HSCT. Two patients developed acute myeloid leukemia. One patient with ankylosing spondylitis had Richter's transformation prior to any CLL therapy. Spondyloarthritis-related disorders were diagnosed in 12 HLA-B27 patients but there was no temporal correlation with development of CLL. Overall survival (OS) and treatment-free survival (TFS) were not significantly different between HLA-B27 patients with or without spondyloarthritis-related disorders. There were no significant differences in clinical characteristics at CLL diagnosis or OS/TFS between HLA-B27 positive and negative patients referred for allo-HSCT.

Conclusions: HLA-B27 positivity does not appear to influence outcome for CLL/SLL patients referred for allo-HSCT. Further studies are needed to evaluate the clinical significance of HLA-B27 in a general CLL population.

1. Introduction

Human leukocyte antigen allele B27 (HLA-B27) is associated with a group of immune-mediated inflammatory disorders, spondyloarthritis (SpA). The different forms of SpA include ankylosing spondylitis (AS), psoriatic arthritis, inflammatory bowel disease related arthritis, and reactive arthritis [1–5]. It has been suggested that those with HLA-B27 have an increased risk of acute leukemia and patients with AS may be predisposed to lymphoid malignancies [6]. However, HLA-B27 has recently been suggested to be protective against chronic lymphocytic leukemia (CLL) by a study on HLA associations with CLL in patients referred for allogeneic hematopoietic stem cell transplantation (allo-HSCT) using the National Marrow Donor Program [7]. Although there have been many studies evaluating the relation between HLA-B27 and

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https://doi.org/10.1016/j.leukres.2019.106193
Received 29 May 2019; Received in revised form 11 July 2019; Accepted 14 July 2019
Available online 15 July 2019
0145-2126/

AS [1–5,8,9], there have been no previous published reports examining the clinical features and outcomes of CLL patients with coincident HLA-B27. One study looked at the outcomes of allo-HSCT for CLL patients based on HLA type but focused on patients with HLA-A1, non-A2 and non-B44 and did not evaluate HLA type at CLL diagnosis or HLA-B27 specifically [10]. Another study showed that the expression of class I major histocompatibility antigens was normal in CLL patients in contrast to the abnormal expression or loss of class I antigens in solid tumours and only 1 in 13 patients with CLL were found to have HLA-B27 [11]. This is consistent with the relatively low prevalence of HLA-B27 in some populations such as a 2–9% prevalence in European and West African populations [8,12]. We sought to compare the clinical characteristics and outcomes of CLL patients referred for allo-HSCT in British Columbia, Canada based on their HLA-B27 status. The hypothesis was that patients with HLA-B27 may have worse outcome than those without HLA-B27, possibly due to their associated comorbidities and possibly due to therapy related concerns.

2. Methods

2.1. Patients

Consecutive patients with CLL or small lymphocytic lymphoma (SLL) who were referred to the Leukemia/Bone Marrow Transplant Program of British Columbia (BC) for pre-transplant work-up including HLA typing between January 1994 and March 2018 were included in this study (N = 279). Clinical characteristics and survival outcomes were compared between HLA-B27 positive and negative patients. Patients with HLA-B27 were identified via HLA typing only; there was no outpatient testing or HLA-B27 specific testing as it is not a routine test performed for CLL patients. Patient data was obtained from the British Columbia Provincial CLL (BCPCLL) Database which houses information on patients with CLL or SLL who have had a referral for cytogenetic testing for CLL fluorescence-in-situ-hybridization (FISH) abnormalities in BC and recently expanded to include all CLL/SLL patients [13]. Routine FISH testing for CLL in BC became available in 2004. FISH testing was performed as previously described [13]. Follow-up data was collected up to April 2018. Hospital records or patient charts from physician offices were also used to gather clinical data. Patient characteristics collected included age; sex; Rai stage, complete blood count and presence of B-symptoms at diagnosis; cytogenetic abnormalities detected by FISH; CD38 status; treatment modalities; other diagnoses of malignancies and follow-up information. Immunoglobulin heavy chain locus mutation status was not included as the test was not available in BC at the time of the study. Further specific clinical information was collected on the HLA-B27 case patients in terms of their specific associated diagnoses.

2.2. Control population

Living solid organ transplant donors and bone marrow donors from BC who were screened for HLA-B27 status with samples collected between 1997 and 2012 were used as a control population for comparison of HLA-B27 frequency with the BC CLL/SLL patient population who were HLA-typed as part of assessment for allo-HSCT.

2.3. Statistics

Comparison of categorical and continuous variables was performed using Chi-square or Fisher's exact tests and Kruskal-Wallis tests, respectively. Overall survival (OS) was defined as time from diagnosis of CLL to time of last follow-up or death from any cause. Treatment free survival (TFS) was defined as time from diagnosis of CLL to time of first treatment for CLL or last follow-up or death if untreated. Survival curves were calculated using the Kaplan-Meier method and compared by log-rank tests [14,15]. Factors compared for impact on survival

Table 1
Patient clinical characteristics and outcomes of CLL/SLL patients who were HLA-typed comparing patients with HLA-B27 and patients without HLA-B27.

Parameter	Data, n (%)		P-value*
	HLA-B27, n = 34	No HLA-B27, n = 245	
Diagnosis			
CLL	28 (82)	212 (87)	0.510
SLL	6 (18)	33 (13)	
Sex, male/female	24/10 (71/29)	170/75 (69/31)	0.887
Age at diagnosis (years), median (range)	53.5 (27–67)	51 (25–71)	0.245
< 60	30 (88)	215 (88)	0.936
≥60	4 (12)	30 (12)	
Ethnicity			
European or Caucasian	31 (91)	143 (58.4)	0.795
Middle Eastern (Persian)	1 (3)	3 (1.2)	
East Asian/Chinese	1 (3)	6 (2.4)	
Native/Mixed Native	1 (3)	2 (0.8)	
Asian Indian	–	5 (2)	
African/Mixed African	–	2 (0.8)	
Filipino	–	3 (1.2)	
Algerian	–	1 (0.4)	
Unknown	0	80 (32.7)	
Rai stage at diagnosis			
0	9 (26)	66 (27)	0.686
I–II	21 (62)	143 (58)	
III–IV	4 (12)	26 (11)	
Unknown	0	10 (4)	
Complete blood cell count at diagnosis, median (range)			
Hemoglobin (g/dL)	136 (100–168)	138 (67–175)	0.829
White blood cell count	19 (2-142)	21 (2-564)	0.704
Lymphocyte count	14 (1-135)	14 (1-558)	0.777
Platelets	182 (82-348)	200 (5-506)	0.144
B-symptoms at diagnosis	5/26 (19)	37/199 (19)	0.937
CLL-specific FISH (highest Dohner category reached)			0.357
17p del	9/25 (36)	54/200 (27)	
11q del	7/25 (28)	41/200 (21)	
Trisomy 12	4/25 (16)	21/200 (11)	
13q del	3/25 (12)	51/200 (26)	
Normal FISH	2/25 (8)	32/200 (16)	
> 1 FISH abnormality present	12/25 (48)	64/200 (32)	0.111
Clonal evolution	3†/25 (12)	33/200 (17)	0.563
CD38 status			
positive	11/20 (55)	72/169 (43)	0.291
negative	9/20 (45)	97/169 (57)	
Richter's transformation	7/34 (21)	25/244 (10)	0.087
Time to Richter's transformation (years), median (range)	5.4 (0.9–21.7)	4.6 (0–16.3)	0.374
Secondary hematological malignancy	4 (12)	19 (8)	0.501
CLL Treatment, first line			
Fludarabine-based	22/33 (67)	154/230 (67)	0.974
Rituximab-based	14/33 (42)	127/230 (55)	0.168
Untreated	1/34 (3)	14/244 (6)	0.499
Second-line CLL treatment	26/33 (79)	186/230 (81)	0.777
Allo-HSCT for CLL	11/34 (32)	119/245 (49)	0.076
HSCT specific Comorbidity Index‡			0.179
0	3 (27)	38 (32)	
1	1 (9)	16 (13)	
2	1 (9)	17 (14)	
3	0	10 (8)	
4	0	8 (7)	
5	2 (18)	2 (2)	
6	0	2 (2)	
Not scored	4 (36)	26 (22)	
Time to Allo-HSCT (years), median (range)	4.6 (1.5–12.4)	5.8 (0.8–28.7)	0.390
Overall survival (years), median (range)	16.4 (1.1–33.8)	13.6 (0.1–42.5)	0.585
Treatment-free survival (years), median (range)	1.4 (0–21.8)	1.3 (0–25.2)	0.855

* p-value comparing HLA-B27 vs. no HLA-B27.

† One patient developed a 17p deletion, one patient developed an 11q deletion and another patient acquired a 13q deletion.

‡ Sorror et al. Blood. 2005;106:2912-2919.

included HLA-B27 status, presence of spondyloarthritis-related features, 17p deletion and allo-HSCT. SPSS version 18 was used to perform statistics.

3. Results

3.1. Patient characteristics

Thirty-four patients (12.2%) who were HLA-B27 positive on pre-transplant work up for CLL (n = 28) or SLL (n = 6) in BC between 1983 and 2012 were identified from 279 CLL/SLL patients who were HLA-typed. The percentage of patients with HLA-B27 was significantly greater than that of 5969 controls tested between 1997 and 2012, 506 (8.5%) were positive for HLA-B27 (p = 0.031). Diagnoses were not available for controls therefore no association with AS could be made. There was no significant difference in patient characteristics at diagnosis between CLL/SLL patients with HLA-B27 and patients without HLA-B27, see Table 1. The median age at diagnosis of CLL in patients with HLA-B27 was 53.5 years (range 27–67) with a male to female proportion of 2.4–1 with no difference compared to those without HLA-B27 (p = 0.887). Twenty-five patients with HLA-B27 had CLL-specific FISH performed with 12 patients having FISH tested prior to therapy and the rest had FISH performed at relapse or prior to allo-HSCT. Seven patients (28%) had an 11q deletion while 9 patients (36%) had a 17p deletion. After a median follow-up of 9.8 years (range, 1.1–33.8 years), three patients with HLA-B27 had clonal evolution with one patient acquiring a 17p deletion, one patient acquiring an 11q deletion and one patient acquiring a 13q deletion.

3.2. CLL treatment

All patients with HLA-B27, except one, received first-line CLL treatment (reflecting the fact that the population tested was being referred for possible allo-HSCT) with 67% being fludarabine-based and 42% rituximab-based. Median age at time of first-line CLL treatment was 56 years (range, 28–67 years) for HLA-B27 patients. Median number of lines of CLL treatment was 3 (range, 1–11). Eleven HLA-B27 patients (32%) received allo-HSCT while about half of patients without HLA-B27 received allo-HSCT (119/245), p = 0.076.

3.3. Spondyloarthritis related diagnoses

Spondyloarthritis or related features were diagnosed in 12 of 34 (35%) of patients with HLA-B27 including AS and supraventricular tachycardia (SVT) in 1, uveitis and monoarticular arthropathy of the knee in 1, Reiter's syndrome in 2 with 1 also having paroxysmal atrial fibrillation, prepatellar bursitis in 1, arthritis in 2, right atrial thrombosis and osteoporosis in 1, mild aortic stenosis and aortic regurgitation in 1, right knee bursitis and cardiac arrhythmias in 1, SVT and eye symptoms in 1 and Wolff-Parkinson-White syndrome and cauda equina syndrome in 1 (see Supplemental Table 1). In some patients the SpA features were diagnosed before CLL and in others were diagnosed after CLL onset.

3.4. Secondary malignancies

Four of 34 (12%) patients with HLA-B27 had a second hematological malignancy including one patient with follicular lymphoma and diffuse large B cell transformation of follicular lymphoma, one patient with multiple myeloma, one patient with acute myeloid leukemia (AML) evolving from myelodysplastic syndrome, and one patient with AML and plasma cell myeloma. This was not significantly more prevalent compared to 19 of 245 (14%) HLA-B27 negative cases with a second hematological malignancy (p = 0.501). Richter's transformation occurred in 20.6% (7/34) of HLA-B27 positive patients (post-CLL treatment in 5, prior to treatment in 2) during follow-up with a median time to transformation of 5.4 years (range, 0.9–21.7 years) vs. 10.2% (25/244) of HLA-B27 negative patients, however no statistical difference was found (p = 0.087). One patient had prolymphocytic leukemia/paraimmunoblastic transformation. Another patient who had AS developed Richter's transformation to a double-hit lymphoma with BCL-2 and C-MYC prior to receiving any therapy for CLL, could not be successfully rescued despite aggressive therapy and died with resistant Richter's. Supplemental Table 1 shows the other diagnoses that patients had in addition to CLL or SLL and their alive or dead status. Eight patients (23.5%) had a second non-hematological malignancy including 6 patients with non-melanoma skin cancer only, 1 patient with renal cell carcinoma and basal cell carcinoma, and 1 patient with papillary thyroid cancer and squamous cell carcinoma of the lung. Twelve of 17 patients had CLL treatment prior to their diagnosis of second primary malignancy or Richter's transformation.

3.5. Overall survival and treatment-free survival

Overall survival of CLL/SLL patients who had HLA-B27, median OS 16.4 years vs. patients who had no HLA-B27 (n = 245), median OS 13.6 years, was not significantly different (p = 0.585), see Fig. 1A. CLL-specific treatment-free survival was also not significantly different between patients with HLA-B27, 1.4 years vs. without HLA-B27, 1.3 years (p = 0.855), see Fig. 1B. There was no difference in OS or TFS between patients with HLA-B27 who had SpA-related features (n = 12) vs. no SpA-related features (n = 22), see Supplemental Fig. 1A and B. When focusing on patients who had 17p deletion, there was a trend for worse OS but no significant difference in HLA-B27 patients (n = 9), median OS 4.8 years vs. patients without HLA-B27 (n = 54), median OS 11.2 years (p = 0.096), see Supplemental Fig. 2A. There was also no significant difference between these groups for TFS, see Supplemental Fig. 2B. Of interest there was no difference in OS between patients who went on to allo-HSCT when comparing patients with HLA-B27 (n = 11) vs. without HLA-B27 (n = 118), p = 0.689, see Supplemental Fig. 3. Comorbidity index scores were compared for patients with data available between 7 HLA-B27 positive patients and 93 HLA-B27 negative patients and there was no difference in scores (P = 0.179) [16]. When the CLL patients who were HLA-typed (n = 279) were compared to patients who were not HLA-typed (n = 1520), OS and TFS were worse in the HLA-typed group, see Fig. 2A and B, reflecting the high risk nature of patients who underwent HLA typing and evaluation for allo-HSCT. There was a trend for better OS for the HLA-typed CLL patients who proceeded to allo-HSCT compared to patients who did not undergo allo-HSCT, median OS 14.8 years vs. 13.4 years (p = 0.081), respectively, see Supplemental Fig. 4.

4. Discussion

The etiology of CLL is unclear but familial risk and genetic predisposition to the disease has been described [17,18]. Susceptibility genes for CLL have been identified from the results of genome wide association studies [19,20]. A recent study showed that a polygenic risk score representing 41 single nucleotide polymorphisms (SNPs) from susceptibility loci was associated with increased risk of CLL and MBL [21]. One large population-based study evaluating the association of HLA alleles with CLL found HLA-B27 to be protective against development of CLL [7], however, there have been no published studies on the clinical features and outcomes of CLL patients with HLA-B27. Thus, we evaluated whether a case series of CLL/SLL patients referred for potential allo-HSCT had a different clinical course if they are HLA-B27 positive. Our data showed that patients referred for allo-HSCT with HLA-B27 did not have inferior outcomes compared to patients without HLA-B27.

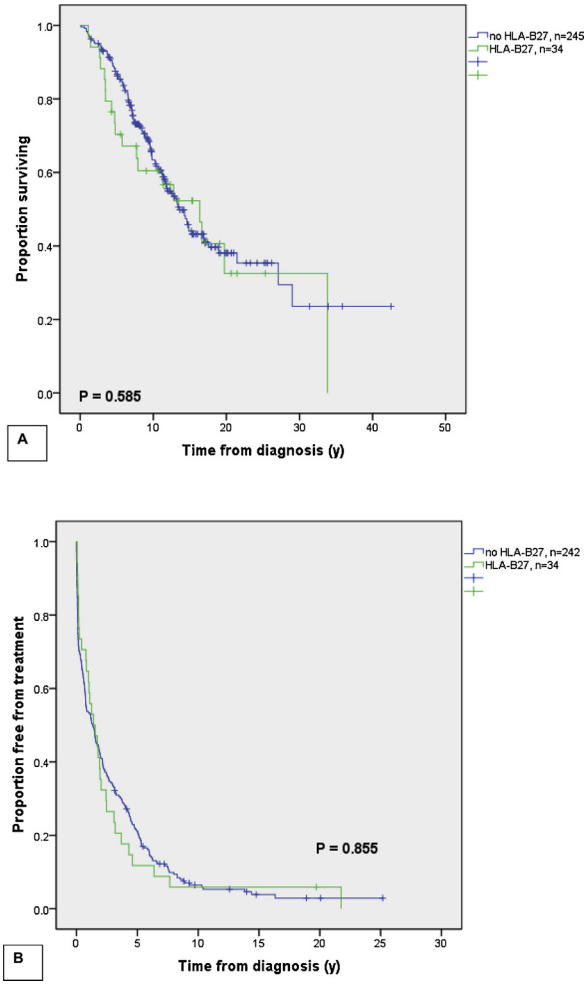

Fig. 1. Overall survival (A) and CLL treatment-free survival (B) from time of CLL diagnosis for CLL/SLL patients with HLA-B27 (n = 34) and patients without HLA-B27 (n = 245). Median OS for patients with HLA-B27 vs. no HLA-B27 was 16.4 years vs. 13.6 years. Median TFS for patients with HLA-B27 vs. no HLA-B27 was 1.4 years vs. 1.3 years.

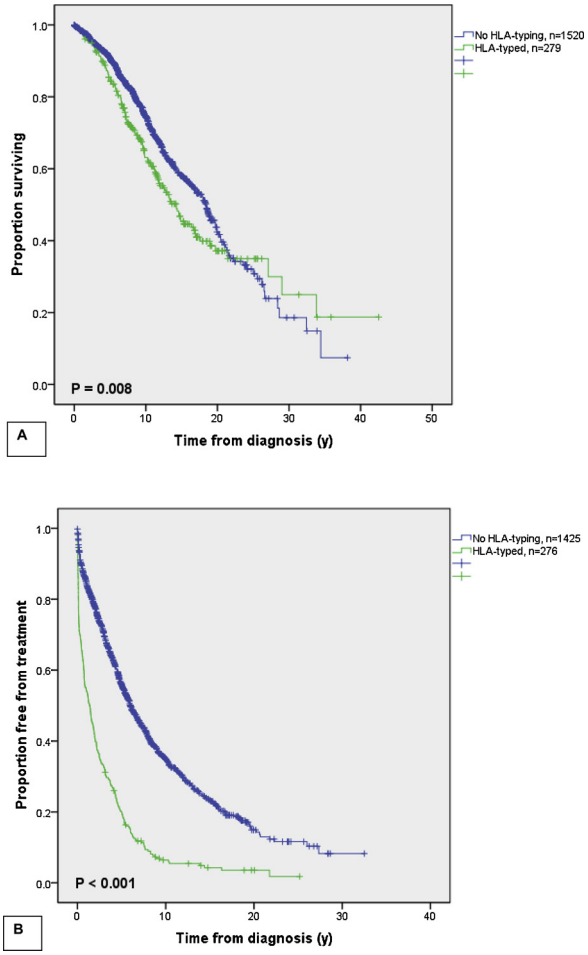

Fig. 2. Overall survival (A) and treatment-free survival (B) from time of CLL diagnosis of CLL/SLL patients who received HLA-typing (n = 279), and patients who did not receive HLA-typing (n = 1520). Median OS for HLA-typed vs. non-HLA typed patients was 14.3 years vs. 18.4 years. Median TFS for HLA typed vs. non-HLA typed patients was 1.4 years vs. 6.0 years.

This was true even for patients who underwent an allo-HSCT suggesting that HLA-B27 positivity does not impact outcomes for younger, higher risk patients.

The case frequency of HLA-B27 in our study of 12.2% was greater than our control frequency of 8.5% and higher than the reported case and control frequencies of 2.7% and 3.5% in Gragert et al. [7] presumably due to the smaller sample size of our cohort and possible bias towards testing patients with SpA-related features. The BC population is 4.5 million with about 63% of the population being Caucasian which is in accordance with the 67% Caucasian make-up of the HLA-B27 patients in our case series [22].

A limitation of our study is that there was selection for patients who were referred for allogeneic stem cell transplant thus our results may not be applicable to the general CLL population. The younger age at diagnosis of CLL/SLL in our case series, similar to the cohort from the National Marrow Donor Program [7] was due to selection bias for patients referred for potential allo-HSCT. The ethnic make-up of our case series being mainly Caucasian is in line with CLL being the most common leukemia in Western populations and less common in African-American and Asian populations even though HLA-B27 prevalence is only slightly higher in Caucasoid (2–18%) vs. Asian populations (5–12%) [12,17,23–25]. The frequencies of high-risk CLL specific FISH abnormalities, 17p (36%) and 11q (28%) deletions were higher in our HLA-B27 cohort group of CLL/SLL patients than that reported in the general CLL patient population of 12% and 11% [26], respectively, and more closely resembled the frequencies observed in CLL allotransplant cohorts as a third of the patients in our series went on to allo-HSCT [27,28]. Similarly, the higher incidence of Richter's transformation in 20.6% of HLA-B27 patients compared to the reported incidence of up to 10% in CLL patients may be attributed to selection of patients for consideration of allo-HSCT [29,30].

There are mixed views on whether to routinely test for HLA-B27 due to questions of its clinical importance as only a small percentage of patients with HLA-B27 will develop spondyloarthritis and high costs of the procedure [9,31]. In our case-series of 34 patients, only 1 patient had AS (3%), and 11 other patients had SpA-related features (32%). There did not appear to be a correlation between onset of SpA-related features and development of CLL or vice versa as some occurred prior to CLL diagnosis in some patients and after CLL diagnosis in others. Another question is whether there is any correlation between HLA-B27 and the risk of secondary malignancies observed in CLL patients. One study in Hong Kong reported HLA-B27 carriers may have an increased risk of acute leukemia and suggested that those with concomitant AS may be predisposed to lymphoid malignancies [6]. One case report showed a patient with AML who developed reactive arthritis and was found to be HLA-B27 positive [32]. Another case report presented a case of AS in a MDS patient with a positive HLA-B27 [33]. Our finding of two patients with HLA-B27 who developed AML and one patient with AS developing Richter's transformation is line with the findings of Au

et al. (2001). There have been reports of increased risk of skin cancer particularly basal cell carcinomas in renal transplant recipients with HLA-B27 [34,35]. Our finding of seven patients with skin cancer confirms the above reports, although there is also increased incidence of skin cancers in patients with CLL [36]. We did not have available data on whether patients were treated for HLA-B27 associated disease with methotrexate or cyclophosphamide or similar. Our finding that patients with prior CLL treatment developing a second primary malignancy or Richter's transformation is in accordance with results of a prior study [37]. Our finding of 32% of HLA-B27 positive patients with a second malignancy seems higher than the reported 17% second cancers in 612 CLL patients in a population-based study conducted in Manitoba however we did not have sufficiently complete data to compare with our whole CLL/SLL population [38].

When comparing CLL/SLL patients who had SpA-related features vs. no SpA-related features, there was no difference in outcome even though AS has been reported to have up to 1.5 times increased mortality compared to the general population [39]. A possible reason for this is that CLL may have had a greater impact on patient mortality than did SpA disease as the cause of death was CLL-related for 15 of 19 patients who died.

HLA-B27 positivity does not appear to influence the clinical course of young patients with aggressive CLL/SLL who are being considered for an allo-HSCT. In addition, having an HLA-B27 does not preclude them from benefitting from transplantation. Therefore routine HLA-B27 testing in CLL/SLL patients may not be warranted. Evidence of good outcome for patients is important when considering risk for CLL therapy and for allo-HSCT. Lack of increased risk of mortality is a positive finding for patients with HLA-B27 and coincident CLL. This information will be valuable for others in assisting with CLL therapy decisions for patients with HLA-B27, including allo-HSCT. A study evaluating HLA-B27 at CLL diagnosis would be needed to confirm whether HLA-B27 protects against CLL. As our study is limited to patients who were referred for allo-HSCT, further studies are needed to evaluate the clinical significance of HLA-B27 in a general CLL population.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We would like to acknowledge the physicians and staff who contributed patient data. We thank the technologists for their work in carrying out the cytogenetic testing of patient samples. We also thank Chao-Yong Lee, data analyst at the Leukemia and Bone Marrow Transplant Program of BC for their help in retrieving HLA data. We thank the Hematology Cell Bank of BC lab personnel who provided HLA data.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.106193.

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