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**No CLL transmission through blood transfusion**

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In this issue of Blood, Hjalgrim et al\(^1\) used the Scandinavian Donations and Transfusions (SCANDAT2) database, which includes comprehensive information on donors and recipients of >20 million blood products handled by the Danish and Swedish blood banks between 1968 and 2010, to address the clinically relevant question of whether chronic lymphocytic leukemia (CLL) is transmitted through blood transfusions.

Specifically, by using the large population-based SCANDAT2 database, the authors identified all donors diagnosed with CLL subsequent to their earliest registered donation (index donors). For each index donor, they identified up to 10 matched donors without CLL at diagnosis of the index donor (control donors). Next they identified all recipients of blood products from the 2 groups of donors and observed them from transfusion with blood from the identified donor until date of CLL, death, emigration, disappearance, or the end of 2012. In their study, they captured development of CLL among all recipients after any particular transfusion between 1980 and 2012. Transfusions were not considered an exposure until after a lag period of 6 months. Taking this approach, they compared CLL incidence rates in the 2 recipient cohorts.

Among 7413 recipients of blood from 796 donors diagnosed with CLL after donation cessation (index donors), 12 recipients (0.2%) were diagnosed with CLL, and among 80 431 recipients of blood from 7477 matched CLL-free donors, 107 recipients with blood from the identified donor until date of CLL, death, emigration, disappearance, or the end of 2012. In their study, they captured development of CLL among all recipients after any particular transfusion between 1980 and 2012. Transfusions were not considered an exposure until after a lag period of 6 months. Taking this approach, they compared CLL incidence rates in the 2 recipient cohorts.

Among 7413 recipients of blood from 796 donors diagnosed with CLL after donation cessation (index donors), 12 recipients (0.2%) were diagnosed with CLL, and among 80 431 recipients of blood from 7477 matched CLL-free donors, 107 recipients (0.1%) were diagnosed with CLL (control donors). Thus, there was no evidence of a statistically altered risk (incidence rate ratio, 0.94; 95% confidence interval [CI], 0.52-1.71) of CLL among recipients of blood from donors diagnosed with CLL after donation cessation. Hjalgrim and colleagues\(^1\) did a supplementary analysis in which they redefined the study exposure as blood donated less than 10 years before donor CLL diagnosis. In this supplementary analysis, the results were not significantly different from the main analysis. On the basis of their results, the authors concluded that there was no evidence of transmission of CLL through blood transfusion.

Prior studies have focused on the relationship between CLL and its precursor state, monoclonal B-cell lymphocytosis (MBL). Interestingly, Shim and colleagues\(^3\) recently found MBL in 149 (7.1%) of 2098 American blood donors age 45 to 91 years, and the prevalence increased with age and male sex. Importantly, in 2009, we were able to study the association between CLL and MBL among 77 469 healthy adults who were enrolled in the nationwide, population-based Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.\(^4\) In that study, we identified 45 patients in whom CLL was subsequently diagnosed (up to 6.4 years later) through the collection of a peripheral blood sample. By using 6-color flow cytometry (with antibodies CD45, CD19, CD5, CD10, k, and l) and immunoglobulin heavy-chain gene rearrangement by reverse-transcription polymerase chain reaction assay, we determined the association between MBL and subsequent CLL and characterized the immunoglobulin gene repertoire of the prediagnostic B-cell clones. On the basis of either flow cytometric or molecular analysis, 44 of 45 patients with CLL (98%; 95% CI, 88%-100%) had a prediagnostic B-cell clone; in 41 patients (91%; 95% CI, 79%-98%), the
The presence of the B-cell clone was confirmed by both methods. The presence of immunoglobulin heavy-chain variable (IGHV) genes was determined in 35 (78%) of 45 prediagnostic clones. Of these clones, 16 (46%) were IGHV3 subgroup genes (including 6 [17%] IGHV3-23 genes), and 9 (26%) were IGHV4 subgroup genes (including 4 [11%] IGHV4-34 genes). Furthermore, 27 (77%) of 35 of the IGHV sequences had mutations, with similar distributions after stratification either below or above the median time between the collection of the prediagnostic blood sample and the subsequent CLL diagnosis. Thus, this definitive prospective screening study shows that B-cell clones (MBL) are early markers for CLL.

Because CLL is consistently preceded by a precursor state (ie, MBL), Hjalgrim and colleagues speculated that perhaps MBL was present in the blood of donors diagnosed with CLL after donation cessation. Consequently, based on their analysis showing no excess of CLL among recipients of blood from donors who were diagnosed with CLL after donation cessation (index donors), they further speculated that transfusion-transmitted MBL does not affect the recipients (eg, transmission of MBL from the donor and progression to CLL in the recipient). However, as pointed out by the authors, because of the wide time window between blood donation and CLL development (up to 32 years), a major limitation of the study, when it comes to evaluating transfusion-transmitted MBL and risk of developing CLL in recipients, is the lack of information regarding donor MBL status (ie, presence or absence of MBL defined by flow cytometry of the blood). Appropriately, the authors state that recipients may have received blood drawn before the donor developed MBL.

Strengths of the study include sample size, data quality, and design. Taking advantage of large population-based databases containing information regarding blood donors and transfusion recipients, Hjalgrim and colleagues used record linkage (through Social Security numbers) with nationwide population and cancer registries to obtain data and study CLL incidence rates in donors diagnosed with CLL after donation cessation vs CLL-free donors.

In summary, based on large numbers, the current investigation shows no evidence of CLL transmission among blood transfusion recipients. Extrapolating from these results, one may speculate that donor MBL transmission also does not increase the risk of MBL and CLL among transfusion recipients; however, original MBL data are needed before we can consider this task completed.

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REFERENCES

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