

TRANSFUSION MEDICINE

No evidence of transmission of chronic lymphocytic leukemia through blood transfusion

Henrik Hjalgrim,¹ Klaus Rostgaard,¹ Senthil K. Vasan,² Henrik Ullum,³ Christian Erikstrup,⁴ Ole B. V. Pedersen,⁵ Kaspar R. Nielsen,⁶ Kjell-Einar Titlestad,⁷ Mads Melbye,¹ Olof Nyrén,² and Gustaf Edgren^{2,8}

¹Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark; ²Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; ³Department of Clinical Immunology, Blood Bank, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark; ⁴Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark; ⁵Department of Clinical Immunology, Naestved Hospital, Naestved, Denmark; ⁶Department of Clinical Immunology, Aalborg University Hospital, Aalborg, Denmark; ⁷South Danish Transfusion Service/Department of Clinical Immunology, Odense University Hospital, Odense, Denmark; and ⁸Hematology Centre, Karolinska University Hospital, Stockholm, Sweden

Key Points

- Transfusion recipients' risk of CLL is not affected by postdonation CLL in donor.
- Recipient CLL does not cluster to individual donors, arguing against MBL transmission.

Monoclonal B-cell lymphocytosis (MBL) is a precursor of chronic lymphocytic leukemia (CLL). Observations of MBL in blood donors raise concern that transmitted MBL may cause recipient CLL. Using a database with health information on 1.5 million donors and 2.1 million recipients, we compared CLL occurrence among 7413 recipients of blood from 796 donors diagnosed with CLL after donation cessation, and among 80 431 recipients of blood from 7477 matched CLL-free donors. During follow-up, 12 and 107 cases of CLL occurred among the exposed and unexposed recipients, respectively, yielding a relative risk of 0.94 (95% confidence interval, 0.52-1.71). Analyses using the entire database showed no evidence of CLL clustering among recipients of blood from individual donors. In conclusion, when donor MBL was approximated by subsequent donor CLL diagnosis,

data from 2 countries' entire computerized transfusion experience over more than 30 years indicate that MBL/CLL transmission does not contribute importantly to recipient CLL risk. (*Blood*. 2015;126(17):2059-2061)

Introduction

Monoclonal B-cell lymphocytosis (MBL) describes the presence of small monoclonal B-cell subpopulations ($<5 \times 10^9$ cells per milliliter) in the peripheral blood of apparently healthy individuals.¹ The MBL cells typically display immunophenotypic characteristics similar to those of chronic lymphocytic leukemia (CLL) to which MBL may progress at rates dependent on the MBL cell count.²

MBL has proved to be fairly common in healthy individuals.² Thus, Shim and colleagues recently identified MBL in 149 (7.1%) of 2098 American blood donors aged 45-91 years, the prevalence increasing with age and male sex.³ The study by Shim et al³ has prompted renewed speculation about the transmission of MBL in blood products potentially causing CLL of donor origin in the recipient.³⁻⁵ Some investigations have added to this concern by suggesting an increased risk of CLL and/or small lymphocytic lymphoma (SLL) among transfused patients.⁶⁻⁸ Meanwhile, other studies observe no or even an inverse association between transfusion and CLL/SLL risk,⁹⁻¹¹ emphasizing that comparisons of transfused patients and nontransfused control subjects are challenging due to fundamental differences between the 2 groups.

We used a binational database with long-term health information on 1.5 million blood donors and 2.1 million of their recipients to evaluate whether potential MBL transmission influences recipient CLL risk. Specifically, we determined if CLL among recipients clustered to individual donors, whether the donors developed CLL

after the donation, and therefore were at increased risk of MBL at donation, or not.

Study design

Our investigation rested on the Scandinavian Donations and Transfusions (SCANDAT2) database¹² and was approved by the regional ethics committees in Stockholm, Sweden, and by the Danish Data Protection Agency. In brief, Danish and Swedish blood banks belong to the public health care sector. SCANDAT2 comprises all available computerized information on donors and recipients of >20 million blood products handled by the blood banks between 1968 and 2010. For all donors and recipients, SCANDAT2 includes information on vital status and health outcomes such as cancer, ascertained in nationwide and essentially complete population and health registers in the 2 countries.¹²

We assessed the possibility of MBL/CLL transmission with whole blood, red blood cell, or platelet products in 2 analyses. In both analyses, the follow-up period was restricted to 1980-2012 for technical reasons relating to coding homogeneity. Information on CLL diagnoses was based on registrations in the Danish and Swedish cancer registers using contemporary national classifications; that is, International Classification of Diseases, Seventh Revision (code 204.1) and 10th Revision (code C91.1).¹³

Taking a look-back approach, we first identified all donors in SCANDAT2 diagnosed with CLL subsequent to their earliest registered donation. For each of these index donors, we identified up to 10 donors without CLL at diagnosis of

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the index donor, matching on age (± 2 years), sex, county, number of donations (± 4), and ABO blood group. We then identified all recipients of blood products from the 2 groups of donors, and followed these from transfusion with blood from the identified donor until date of CLL, death, emigration, disappearance, or end of 2012. We compared CLL incidence rates in the 2 recipient cohorts by Poisson regression. In supplementary analyses, we redefined the study exposure as blood donated <10 years before donor CLL diagnosis. Because incipient CLL may necessitate transfusion, transfusions were not considered an exposure until after a lag period of 6 months. We also specifically analyzed transfusions before 1997 when leukocyte depletion was very uncommon.

Theoretically, transfusion-transmitted MBL might progress to CLL in recipients without doing so in the affected donor. We therefore also investigated whether CLL clustered among recipients of blood from individual donors irrespective of their individual CLL status. To this end, we characterized the occurrence of CLL among all recipients after any particular transfusion between 1980 and 2012 according to age, sex, country, and calendar period. This method allowed us to estimate the number of CLL cases expected to occur among the recipients of each individual donor's blood. To identify potential CLL clustering, we then compared the expected and observed numbers of CLL cases among the individual donors' recipients. Assuming a Poisson distribution of number of CLL cases, the overall comparison was performed using a χ^2 goodness-of-fit test.

Results and discussion

The analyses provided little evidence that donor MBL/CLL transmission in blood products influences recipient CLL risk. In the look-back analysis, in which donor MBL was approximated by CLL diagnosis, we identified 7413 recipients of blood from 796 donors who later developed CLL ("exposed recipients"), and 80 431 recipients of blood from 7477 donors free of CLL at index-donor diagnosis ("unexposed recipients"). During follow-up, 12 and 107 CLL cases occurred among the exposed and unexposed recipients, respectively, yielding an incidence rate ratio of 0.94 (95% confidence interval [CI], 0.52-1.71). When exposure was redefined as blood donated <10 years before donor CLL diagnosis, the incidence rate ratio was 0.46 (95% CI, 0.12-1.85). Results were also largely similar in the preleukocyte depletion era (incidence rate ratio 0.86 [95% CI, 0.42-1.79]). Analogously, there was little indication of CLL clustering among recipients of blood from individual donors (Table 1).

Our study adds considerably to the literature on CLL transmission in blood products. Aside from failed attempts to transplant CLL from donors to volunteer recipients in historical small-scale experiments,^{14,15} transfusion transmission of CLL has been assessed in only 1 follow-up study of 15 patients, none of whom developed CLL after receiving blood from 5 donors who subsequently developed CLL.¹⁶

Strengths of our investigation include both data quality and design. We took advantage of linked information about blood donors and transfusion recipients, mandatorily registered by Danish and Swedish blood banks. Using the unique personal identification number issued to all residents in the 2 countries as key, we ascertained information about vital status and cancer outcome among donors and recipients from nationwide population and cancer registries.¹² We then assessed CLL risks only among recipients, thereby avoiding confounding by indication that is common to comparisons of transfused and non-transfused groups. Moreover, in Scandinavia, allocation of blood products is governed essentially only by blood group and geographical proximity of donor and recipient. Consequently, both of our analytical approaches rested on virtually random recipient exposure allocation and were therefore unlikely to be confounded.

Table 1. CLL clustering among recipients of blood from individual donors

Cases of CLL	Observed	Expected	Observed/expected*
0	1416610	1416593.42	1.00 (1.00-1.00)
1	8535	8567.82	1.00 (0.98-1.02)
2	87	71.09	1.22 (0.98-1.50)
3+	1	0.66	1.51 (0.09-6.66)

*Observed and expected frequency mutual ratios, with 95% likelihood ratio–based CIs shown in parentheses. $P_{\text{homogeneity}}$ for observed/expected ratios = .31.

Study limitations include absence of actual donor MBL status, for which we instead used postdonation CLL diagnosis in the look-back analyses. Although MBL presumably invariably precedes CLL,¹⁷ it is likely that some recipients in the look-back analysis received blood drawn before the donor developed MBL. However, the supplementary analyses, less likely to be affected by such misclassification, also showed no evidence of MBL/CLL transmission. Scandinavian donors were until recently deferred from donation at age 65 years.¹⁸ Because both MBL prevalence² and CLL incidence increase with age, we cannot exclude that blood products from older donors confer greater recipient CLL risk than our analyses suggest. Because donor cell engraftment most likely is also dependent on transfusion circumstances and recipient immune status,^{19,20} we also cannot exclude variation in recipient susceptibility to transfusion-transmitted MBL/CLL. Finally, the introduction of leukoreduction in Scandinavian blood banks during the study period may have reduced our ability to detect MBL/CLL transmission.

In conclusion, resting on the entire computerized transfusion experience in 2 countries during more than 30 years, our analyses provide no evidence that donor MBL/CLL transmission contributes significantly to CLL risk among transfusion recipients.

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Authorship

Contribution: All authors were involved in data acquisition; H.H., K.R., and G.E. designed the study, analyzed the data, and drafted the manuscript; and S.K.V., H.U., O.B.V.P., K.-E.T., C.E., K.R.N., O.N., and M.M. provided statistical expertise, critically revised the manuscript, and approved the final version of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Henrik Hjalgrim, Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, DK 2300 Copenhagen S, Denmark; e-mail: hhj@ssi.dk.

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