Progress in Transplants for Acute Lymphoblastic Leukemia

Robert Peter Gale

SUMMARY

Hematopoietic cell transplants are used to treat some adults with acute lymphoblastic leukemia, especially those with high-risk features, such as those with *BCR::ABL1*. This strategy may be changing given the safety and efficacy of modern tyrosine kinase inhibitors. Although these transplants are often successful, leukemia relapse remains the dominant cause of transplant failure. There are several approaches to this problem discussed by the authors of a recent article in the journal. The good news is therapy of recurrent leukemia posttransplant seems increasingly successful and for diverse reasons, survival is increasing substantially.

See related article by Bazarbachi et al., p. 1004

In this issue of *Clinical Cancer Research*, Bazarbachi and colleagues interrogated an observational database of the European Bone Marrow Transplant Group to determine whether there was a change in survival in persons with Philadelphia chromosome–positive acute lymphoblastic leukemia (ALL) in first complete remission relapsing after a first allogeneic hematopoietic cell transplant 2000–2019 (1). The authors report 2-year postrelapse survival increased from 28% in 2000–2004 to 55% in 2015–2019. The predominant vector explaining this improvement is a decrease in the risk of deaths from leukemia among those who died, 72% in 2004–2004 to 55% in 2015–2019 (cumulative incidences of relapse were not reported).

This improvement is exciting and the authors suggest it likely results from more effective postrelapse interventions including tyrosine kinase inhibitors (TKI), bispecific antibodies such as blinatumomab and inotuzumab ozogamicin, better supportive care, increasing use of a second allotransplant, possibly quantifying numbers of remaining leukemia cells by measurable residual disease (MRD) testing and, most recently, use of CAR-T cells (2).

Whenever we use an observational dataset to study time-dependent changes in an intervention, we need to know what other covariates might have changed besides the intervention being studied. Potential confounders are displayed in **Fig. 1**. For example, were persons transplanted in first complete remission in 2000–2004 identical to those transplanted in in 2015–2019? Certainly, our definition of complete remission has evolved with the recent definition of complete remission in *BCR::ABL1*–related ALL now including undetectable MRD by qRT-PCR detection of *BCR::ABL1* mRNA transcripts. If people receiving a transplant are differently defined as being in complete remission at different times, we might expect different outcomes upon relapse. The authors avoided this problem by including only subjects in histologic complete remission disregarding results of MRD testing.

Another covariate is therapy used to achieve a complete remission. During the interval being studied, this has also evolved from mostly chemotherapy to chemotherapy with TKIs and most recently, to TKIs alone (2). Can we equate someone in complete remission after chemotherapy with someone in complete remission after only TKI therapy? Probably no. Some other changing covariates reflect selection biases. For example, some experts think only persons in histologic complete remission who are MRD test–negative benefit from an allotransplant and would not transplant someone who was MRD test–positive (3). Unsurprisingly in the art rather than science of medicine (if it exists), other experts believe the contrary. The sum of these considerations make it unlikely someone relapsing after an allotransplant 2015–2019 is identical to someone relapsing after an allotransplant 2000–2004.

Another potential confounder of this analysis is length time bias (4). Consider identical subjects transplanted in complete remission at the same time both of whom who relapse and in whom you want to determine postrelapse 2-year survival. Subject 1 is determined to have relapsed after a remission duration of 1.5 years based on the >5% bone marrow blasts. Subject 2 would have had a similar remission duration if relapse was also determined by bone marrow blasts but here relapse was declared 6 months earlier based a positive MRD test. When we examine postrelapse survivals, subject 2 will have appeared to have a 6 month briefer remission compared with subject 1 even though they would have the same relapse endpoint using relapse definition. Now, what if we are studying a specific postrelapse endpoint, say 2-year survival? If subject 1 dies 1.75 years after relapse, he will not be a 2-year survivor whereas subject 2 will be. The implication of length time bias is obvious. By using only histologic relapse as the endpoint, the authors avoided this potential bias. Several issues in defining endpoints are reviewed elsewhere (5).

The next question is whether we can adjust for potential confounders in analyses of an observational database. The answer is yes and no. Posttransplant relapse survival prediction models have Concordance statistics in the range of 0.7, meaning, they are better than flipping a fair coin but very far from ideal. What about other methods such as matched-pair analyses and propensity score matching? Better, but we can only match for predictive or prognostic covariates we know about. Unfortunately, this is probably only about one half of the universe of predictive and prognostic covariates. These limitations are why we do randomized controlled trials, a technique clearly not applicable to the question the authors are studying.

It is important to emphasize the improved survival that the authors describe does not reflect increased transplant antileukemia efficacy but

Centre for Hematology Research, Department of Immunology and Inflammation, Imperial College London, London, United Kingdom.

Corresponding Author: Robert Peter Gale, Centre for Hematology Research, Department of Immunology and Inflammation, Imperial College London, London SW7 2AZ, United Kingdom. Phone: 908-656-0484; Fax: 310-388-1320; E-mail: robertpetergale@alumni.ucla.edu

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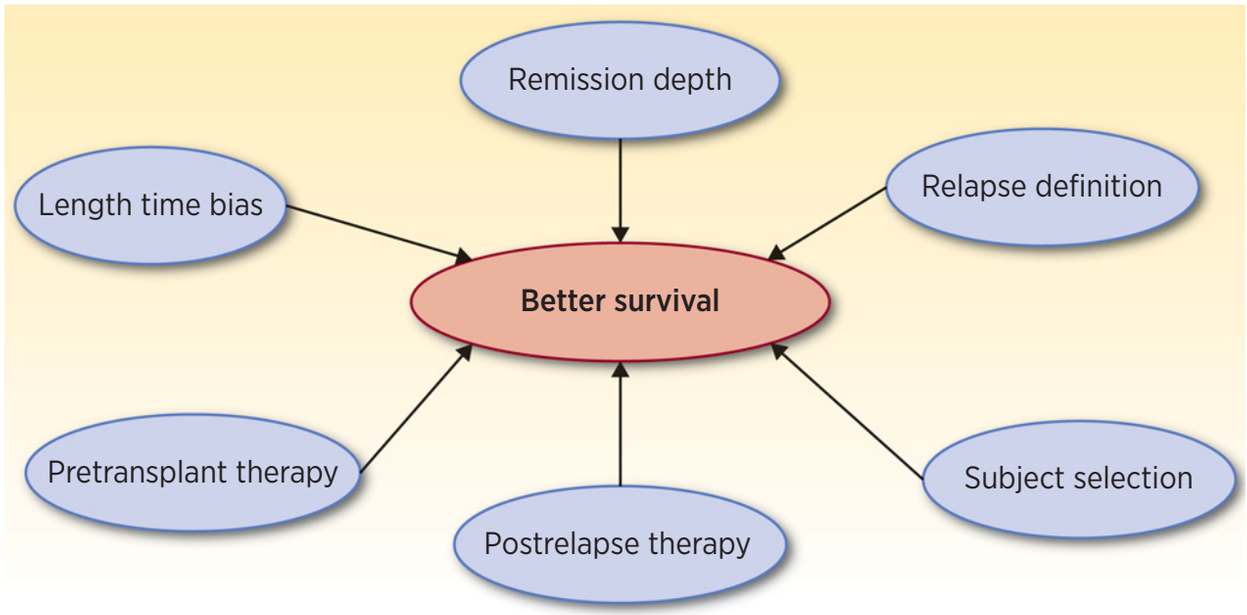

Figure 1.
Causes and potential confounders explaining increased postrelapse survival after transplants for Philadelphia chromosome–positive acute lymphoblastic leukemia in first complete remission.

rather the survival of persons who relapse posttransplant. As such, we are looking at a selected posttransplant cohort, those relapsing and not everyone receiving a transplant for this indication 2004–2019. Persons not relapsing but, more importantly, persons dying of competing causes such as transplant-related mortality (TRM), graft-*versus*-host disease (G*v*HD), interstitial pneumonia, and other infections before relapsing are excluded for this dataset. Some of these events are presumably unrelated to relapse risk–like TRM and interstitial pneumonia but there is confounding between relapse risk and GvHD: severe GvHD is associated with a decreased relapse risk but may kill the victim such that we cannot know whether they might relapse if they survived. This means improvements in our ability to prevent and/or control GvHD posttransplant over the 2000–2019 interval such as use of posttransplant cyclophosphamide impact which persons are in the relapse population the authors are studying. And there is also the impact of donor type with some donor types more likely to cause G*v*HD compared with the others.

This raises another important consideration. The authors describe increasing use of less intensive pretransplant conditioning regimens typically termed reduced-intensity conditioning (RIC) which are associated with increased leukemia relapse risk compared with more intensive pretransplant conditioning regimens in most studies. It is reasonable to postulate leukemia relapsing after more intensive pretransplant conditioning regimens commonly used in the early years of this study are likely to be more aggressive than those relapsing after receiving a RIC pretransplant regimen. This change in leukemia cell biology alone could explain improved postrelapse survival without invoking improvements in postrelapse therapies suggested by the authors. Another issue is the changing definition of leukemia relapse during the study interval. For example, in 2000–2004 most relapses were defined by reappearance of lymphoblast in blood and/or bone marrow. However, in the 2015–2019 relapse is sometimes defined by a positive MRD test result. Putting aside the issue of a possible false-positive MRD test, this difference would result a length time bias favoring the impression of longer survival in the 2015–2019 cohort. The authors avoided this potential bias by only including subjects with histologic relapse ignoring relapses defined by MRD testing. However, physicians are free to intervene when a positive MRD test is detected perhaps averting histologic relapse. This cannot be controlled for in an observational database.

The authors cite younger age at relapse, longer interval from transplant to relapse, achieving a second remission and receiving a 2nd transplant as the main covariates correlated with better survival. These covariates are also correlated with more favorable leukemia cell biology confounded by different definitions of leukemia relapse.

In their Discussion, the authors cite their study as: a retrospective analysis of a homogenous cohort of 899 patients. For reasons I discuss above, we should be cautious accepting this claim. Elsewhere in the Discussion the authors state: the majority of posttransplant relapses in Ph+ ALL are the result of the emergence of ABL kinase domain (KD) mutations citing two studies by Soverini and colleagues (refs. 26 and 27). However, the cited studies do not support this conclusion and the frequency of *ABL1* kinase domain mutations associated with posttransplant relapse in this setting is unknown.

The increased postrelapse survival of transplant recipients following leukemia relapse is welcome news and the authors are to be complemented for studying this outcome in a large cohort. However, there are several reasons why survival might have increased and which, unfortunately cannot be sorted out by analyzing data from an observational database spanning almost 20 years. The danger is incorrectly attributing this improvement to ineffective postrelapse interventions, thereby encouraging their use. However, regardless of why, patients and physicians will be grateful for the good news these authors bring.

Author's Disclosures

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