Comment on Hovorkova et al, page 2771

CML in blast crisis: more common than we think?

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In this issue of Blood, Hovorkova and colleagues assessed minimal residual disease (MRD) sequentially in children with Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) via BCR-ABL1 genomic polymerase chain reaction (PCR) and immunoglobulin gene (IG)/T-cell receptor gene (TCR) PCR in parallel. Results were concordant in most patients, but >20% of children with Ph+ ALL had MRD levels that were >1 log higher with BCR-ABL1 genomic PCR than with IG/TCR PCR. Using cell sorting and fluorescence in situ hybridization (FISH) to study patients with discordant MRD results, the authors demonstrated conclusively that BCR-ABL1–positive cells were present in nonmalignant B cells, T cells, and myeloid cells, establishing that the translocation occurred in a multipotent hematopoietic progenitor cell and suggesting that these patients have a disease more akin to chronic myeloid leukemia (CML) in lymphoid blast crisis than Ph+ ALL.

The discovery of the “Philadelphia chromosome” in patients with CML by Peter Nowell and David Hungerford almost 60 years ago, followed by the recognition that this abnormal chromosome was a reciprocal t(9;22)(q34;q11) that produced a chimeric BCR-ABL1 fusion protein that is a constitutively active tyrosine kinase, and development of imatinib and related tyrosine kinase inhibitor (TKI) therapy established the foundation for precision cancer medicine. We know now that BCR-ABL1 fusion defines CML and is also present in 5% of pediatric and 25% of adult ALL. Treatment with imatinib and related TKIs has converted CML from a deadly malignancy to a disease that can be managed chronically, and adults with CML now have an expected lifespan approaching that of the general population. Ph+ ALL was once considered the deadliest form of pediatric ALL, but addition of TKI therapy to intensive chemotherapy has improved cure rates substantially and obviated hematopoietic stem cell transplant (HSCT) in most cases. Nevertheless, still new findings emerge that change our understanding of these diseases.

The distinction between Ph+ ALL and CML is usually clear. We know that CML in lymphoid blast crisis can “masquerade” as Ph+ ALL in some cases, but it is generally felt that these account for a very small minority of Ph+ ALL cases. In the most extreme example, patients can “relapse” with CML in chronic phase following treatment of what was initially diagnosed as Ph+ ALL, thereby unmasking the original diagnosis as CML in lymphoid blast crisis. Other patients are recognized that may be analogous to those described by Hovorkova; they attain remission with low or negative MRD (as defined by flow cytometry or IG/TCR PCR) at the end of induction therapy, but have persistence of the Philadelphia chromosome at levels ≥1% via standard karyotype analysis or FISH. The Children’s Oncology Group has identified a few such patients on each of their recent Ph+ ALL clinical trials and has considered them to have CML in lymphoid blast crisis.

The findings reported by Hovorkova show that this is not a rare occurrence at all. Although more studies are needed, these data might have substantial clinical implications. The current thinking is that any patient with CML that presents in or develops blast crisis needs HSCT for cure. Although this is not established definitively, it is standard clinical practice. We know that many children with Ph+ ALL can be cured without HSCT; in some cases, patients have a very poor response to initial therapy and clearly need something more than chemotherapy plus TKI for cure. Whether that “something” is HSCT or other therapies is a question for another day. However, there are other patients with Ph+ ALL that appear to respond very well to initial treatment with chemotherapy plus TKI, but later experience relapse. Relapse happens in all subtypes of ALL, but there are suggestions that the relapse risk in patients with an excellent MRD response, as measured by flow cytometry or IG/TCR PCR, is much higher in Ph+ ALL than other ALL subtypes and that MRD might be less predictive of outcome in Ph+ ALL. These data have been hard to interpret due to small numbers, but the current report suggests an alternative hypothesis. Among patients in the current study with discordant MRD as assessed by genomic BCR-ABL1 PCR and IG/TCR MRD, 10/12 who underwent HSCT are alive as compared with only 1/3 treated without HSCT. In contrast, survival seemed similar in those with concordant MRD whether they received HSCT or chemotherapy plus TKI.

Although the numbers are very small, these data suggest that patients presenting with “Ph+ ALL” may comprise 2 subpopulations. The majority has a disease analogous to other ALL subtypes, with the sentinel BCR-ABL1 fusion

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confined to B-lymphoid cells. In contrast, another subset of patients, perhaps accounting for 20% to 25%, may have a disease in which the sentinel Philadelphia chromosome and BCR-ABL1 fusion occurred in a multipotent progenitor cell. Treatment with chemotherapy and a TKI may eliminate the bulk disease in the lymphoid clone, producing an excellent MRD response when measured by conventional MRD methodologies, but leaving a reservoir of Ph+ cells in other lineages.

Much more work is needed to understand these findings and particularly their clinical implications. The current study challenges us to perform these studies so that we can understand the frequency of “Ph+ ALL” subtypes that have multilineage involvement vs disease restricted to the lymphoid lineage and the clinical implications of these differences. Understanding the different potential subtypes of Ph+ ALL is particularly relevant to adults with Ph+ ALL because this subtype comprises a much higher percentage of adult than pediatric ALL, and because HSCT remains the most commonly used approach for adults with Ph+ ALL.9

As observed by the philosopher Roseanne Roseannadanna, “It just goes to show you, it’s always something—if it ain’t one thing, it’s another.”

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REFERENCES


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THROMBOSIS AND HEMOSTASIS

Comment on Curtis et al, page 2793

At last: evidence rather than emotion

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Perinatal stroke is often a devastating and unexpected event for families that leads them to ask the question of “why?” The study by Curtis et al1 in this issue of Blood suggests that the answers to this question are not to be found in standard thrombophilia testing.

Thrombophilia, a broad term inclusive of a variety of disorders, has variably been shown to be associated with venous thromboembolic diseases in adults, although the link to arterial disease is more tenuous. Currently, most guidelines support very limited clinical usefulness of thrombophilia testing in adult populations.2 The data supporting thrombophilia testing in neonatal or perinatal stroke is far from convincing. One could reasonably extend that statement to childhood stroke and potentially childhood thrombosis in general.3 Previous studies of dubious quality have suggested a potential association with perinatal stroke, however, none have demonstrated any impact of testing on recurrence rates, clinical outcome, or future therapy.4 Although some studies have suggested a link to neurological outcome, most would argue the recommended follow-up and interventions are unchanged by the results of thrombophilia testing. Yet thrombophilia testing is frequently performed in this situation. Many clinicians, in an attempt to provide some answers for desperate parents, embark on testing knowing that the interpretation of any positive results is fraught with uncertainty. Testing is often driven by parents who have been scouring the internet for answers and come asking about thrombophilia. Childbirth is supposed to be a time of great joy. An unexplained perinatal stroke that will likely have lifelong significant consequences for the infant is incredibly challenging for parents.

There are issues of their fears for their child, their unfounded feelings of guilt, as well as concerns about the risks for future children. Thus, the potential impact of performing tests of unknown significance for the child’s future, and, indeed, for future children in the family, is arguably more negative than positive because it may increase unfounded fears, leading to overtreatment and inhibitions or restrictions on the child. Until now, clinicians have not had quality data to support making an argument to parents against doing such testing.

Curtis et al performed a prospective, population-based, controlled, disease-specific study that suggests minimal association between perinatal stroke and thrombophilia (specifically, a broad range of thrombophilia markers). The authors make the relevant point that this does not exclude a role of disordered coagulation in the etiology of the event, but that such a role is unlikely to be found by testing standard thrombophilia assays. Such a view is entirely consistent with our knowledge of developmental hemostasis.5 The coagulation system changes rapidly in the first few days of life. In fact, the whole plasma milieu is fundamentally different when comparing neonates and adults.6 Placental-released glycosaminoglycans probably contribute to the overall balance of coagulation, and yet these factors are no longer detectable after the first week of life.7 A much greater understanding the coagulation system in the placenta, fetus, and
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