The model presented by Bernitz et al ties together many earlier observations. It explains why bone marrow HSCs seem to be severely compromised immediately after G-CSF treatment. Furthermore, the article helps resolve a paradox that surrounds the effects of G-CSF on HSC self-renewal. Many hematopoietic stresses, such as blood loss, infection, inflammation, or chemotherapy, can induce HSC proliferation. In those cases, sustained proliferation correlates with a decline in functional HSCs that is often described as “HSC exhaustion.” Although G-CSF has been shown to induce HSC proliferation and transiently impair HSC function, it does not appear to permanently deplete the HSC pool. Cessation of the cytokine allows bone marrow HSC function to return to normal. An explanation for this difference, provided herein, is that G-CSF–stimulated LR-HSCs do not actually divide extensively, and proliferation is largely restricted to nonselfrenewing populations. This finding aligns well with a recent study by Kovtonyuk et al, and it is good news from a clinical perspective because it suggests that G-CSF treatment will not deplete the dormant HSC pool in human stem cell transplant donors.

The Bernitz et al study does raise additional questions. It is not clear why LR-HSCs mobilize more efficiently than nonLR-HSCs. The authors suggest proximity to the vasculature as one potential mechanism. Differences in the expression of surface proteins that regulate mobilization and homing (eg, VLA-4 or CXCR4) might also contribute. It is also not clear why LR-HSCs are refractory to the mitogenic effect of G-CSF or why some committed progenitors (eg, most colony-forming progenitors) mobilize efficiently, whereas other committed progenitors (eg, CD41+ phenotypic HSCs) do not. Finally, the study raises the question of whether other mobilizing regimens, such as AMD3100, will also selectively mobilize LR-HSCs. Although further studies are needed to address these questions, the study by Bernitz et al provides an important framework for understanding how G-CSF regulates mobilization and proliferation in subpopulations of phenotypic HSCs. The concepts presented in their article will shape future efforts to improve HSC mobilization regimens in humans.

REFERENCES


CLINICAL TRIALS AND OBSERVATIONS

Comment on Landier et al, page 1919

Self-reported adherence in ALL: true or false?

Karen R. Rabin

In this issue of Blood, following their seminal report on the risk of relapse associated with nonadherence to oral 6-mercaptopurine (6MP) during maintenance therapy for childhood acute lymphoblastic leukemia (ALL), Landier et al here investigate whether patient self-report is a reliable measure of 6MP adherence.

Unfortunately, the data suggest that relying on self-report is not sufficient when estimating adherence in this population. This is an important extension of their previous reports that indicated nonadherence is prevalent during ALL maintenance therapy, and that relatively minor degrees of nonadherence have a significant adverse impact on survival. The current report also bears unfortunate news, this time regarding the prevalence of patient overreporting of 6MP adherence. This report and others from this group present data from a large (n = 416) prospective Children’s Oncology Group study in which patient adherence to oral 6MP was tracked for a period of 6 months per subject during ALL maintenance therapy. Electronic monitoring was performed by supplying 6MP to subjects in bottles with a medication event monitoring system (MEMS) TrackCap which recorded the time and date of each bottle opening. Self-report was assessed by patient/parent questionnaire at 4 time points over the 6-month study period.

In their initial study, Bhatia et al reported a progressive increase in relapse with decreasing adherence for all levels of adherence below 95%, a decline in mean adherence for all patients over the 6 months of study participation, and a significantly lower mean adherence among Hispanics compared with non-Hispanic whites (88.4% vs 94.8%; P < .001). They subsequently reported that adherence rates were also significantly lower in African Americans (87%) and Asian Americans (90%), and again confirmed a significantly higher risk of relapse associated with 6MP nonadherence. In light of the increased risk of relapse associated with 6MP nonadherence,
identifying nonadherent patients is vital for designing and implementing targeted interventions. As electronic monitoring is expensive and labor-intensive, Landier et al compared this approach to the utility of self-report data collected by questionnaire. They assigned patients to 4 categories: “perfect reporters” (matching self-report and electronic record; 12% of the cohort), “overreporters” (self-report exceeded electronic record by ≥5 days in at least half the study months; 23.6% of the cohort), “underreporters” (self-report less than electronic record in all study months; 0.3%), and “other” (remainder; 63.9% of the cohort). Overall, a striking 84% of patients overreported 6MP intake at least once (see figure). Although this figure indicates that some degree of overreporting is widespread, Landier et al focus primarily on identifying features associated with the extreme overreporting phenotype defined above and identified in about one-quarter of patients. They found that overreporting was significantly associated with 6MP nonadherence, non-white race (with a significant association for each group: Hispanics, Asians, and African Americans), and lower paternal education. Finally, they provide a calculation of the sensitivity and specificity of self-reported adherence. The specificity of self-report to detect adherence is an encouraging 95.8%, that is, patients who are adherent are unlikely to self-report nonadherence. However, the sensitivity of self-report to detect nonadherence is only 52.7%, reflecting the fact that a sizeable number of nonadherers self-report that they are adherent.

This study contributes importantly to our understanding of adherence in childhood ALL. Specifically, it points to the inability to rely solely on self-report as a measure of adherence. Unfortunately, this is consistent with findings from studies of self-report in other chronic childhood illnesses. Strengths of the study design include that it is a large, prospective, multisite trial with a racially and ethnically diverse population, and that it utilizes optimal objective measures of adherence in the form of both the MEMS TrackCap system and red cell thioguanine nucleotide levels. The use of monthly questionnaires as a measure of self-reported adherence is vulnerable to several potential biases (eg, measurement bias and social desirability bias). However, given the consistency of findings on self-report in the literature based on a variety of measures, it seems unlikely that an alternative self-report measure would have resulted in substantially more accurate self-reporting.

Given the richness of the data collected on this study, it is a minor disappointment that this report focuses predominantly on characterizing the overreporter group, as there are likely additional insights to be gained from analyses of the nearly two-thirds of patients relegated to the broad “other” category. Nevertheless, the core findings regarding the unreliability of self-reported adherence and the characteristics associated with overreporting are valuable.

What are the next steps in attacking the challenge of treatment nonadherence in childhood ALL? The authors point to a prediction tool which they are developing to identify patients at risk for nonadherence. Other valuable work is under way to develop interventions designed to enhance adherence. Given the widespread prevalence of nonadherence, and the risk of relapse associated with relatively minor degrees of nonadherence, I would argue that the work from this group provides a compelling rationale for developing broad-based interventions to improve adherence universally among all patients, in addition to identifying extreme overreporters for specific additional targeted interventions. Perhaps more importantly, it is clear from these studies of nonadherence and its impact on relapse that developing interventions for nonadherence deserves the same prioritization of research effort as investigations of novel anticancer therapies.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


DOI 10.1182/blood-2017-02-767525

© 2017 by The American Society of Hematology
Self-reported adherence in ALL: true or false?

Karen R. Rabin