with higher levels of minimal residual disease (MRD). Secondary mutations involving RTKs are common in CBF AML and have been reported to be prognostic alone (eg, KIT) or in combination (eg, KIT, RAS, FLT3). Other articles associate inferior outcome not with presence of RTK mutations but with their allelic burden. Although epigenetic (eg, ASXL2), cohesin and other types of mutations have been associated with worse outcomes in CBF AML, the presence of these mutations did not erase the poorer impact of clonal interference in their analysis.

Clonal interference, initially implicated in asexually dividing populations, is defined as the simultaneous spread of multiple beneficial mutations in a population in contrast to the traditional view of rare beneficial mutations that survive drift and increase in frequency. Clonal interference indicates movement of multiple mutations as temporal clusters within a population thus escaping selection drift. One potential limitation of the analysis by Itzykson et al is that the presence of clonal interference is inferred on the basis of the coexistence of multiple RTK mutations and not single-cell sequencing.

Quantitative monitoring of MRD has been one of the most important prognostic parameters in CBF AML, because the presence of unique translocations make this subgroup of AML amenable to molecular monitoring of MRD. Although MRD after 2 cycles of treatment was not impacted by presence of clonal interference in the analysis by Itzykson et al, MRD data were available in a smaller cohort (limited to after 2 cycles of therapy) and were included in a bivariate analysis only. Thus, the question of whether clonal interference is prognostic completely independent of serial MRD data has not been answered.

Effective treatment can overcome the impact of prognostic factors. In CBF AML, more intensive regimens have resulted in very impressive relapse-free survival but no overall survival. This raises the question, Can such regimens overcome the adverse impact of clonal interference in a genetically less complex disease such as CBF AML, which is considered sensitive to high-dose nucleoside analogs? The variability of number and intensity of consolidation therapies in the article by Itzykson et al limits the ability to answer this question.

Their article brings up more interesting biological questions. CBF AML is generally considered to have a less complex genomic architecture and have good outcomes with standard high-intensity chemotherapy. Thus, their article is important in highlighting the impact of intratumoral heterogeneity in a leukemia with a relatively simple genomic background. The higher risk of relapse with clonal interference raises 3 possibilities: high overall RTK mutation burden, a subset of mutations that are resistant to chemotherapy, and mutational instability. Although other articles associate higher allelic burden of RTK mutation with worse outcome, which implies the importance of the first possibility, the authors have tried to rule out the first possibility by showing that VAF does not matter and the second possibility by bootstrapping analysis, and they suggest that clonal interference is a likely proxy for mutational instability. Conceptually, these findings also pose the challenge of unearthing vulnerabilities of mutational architectures rather than single mutations. Single-cell sequencing of residual disease or serial sequencing of uniformly treated cohorts may answer some of these questions.

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REFERENCES


TRANFUSION MEDICINE

Comment on van der Meer et al, page 223

Progress with pathogen-reduced blood

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In this issue of Blood, van der Meer et al1 make an important contribution to the further adoption of pathogen reduction technology (PRT), a new paradigm to improve the safety of transfused blood products,2 into clinical practice.

There are three PRT technologies, all of which are based on damaging nucleic acids and thus preventing replication of contaminating infectious agents. The ability of PRT to inactivate pathogens is primary, but the PRT must also maintain the clinical effects of the blood products. The trial by van der Meer et al was carried out over 6 years at 10 sites in 3 countries; it was prospectively randomized and
controlled, and it compared usual platelets with riboflavin UV light–treated PRT platelets. A total of 460 patients was enrolled into 567 transfusion treatment periods (284 patients received PRT and 283 received usual platelets). Platelets were prepared from whole blood by the buffy coat method, which is widely used worldwide, but not in the United States. Platelets were suspended in plasma and leukoreduced. Pooling of platelets from several units of whole blood produced a platelet dose similar to that used in the United States, although the number of units of whole blood pooled differed among the countries.

Although the study was conducted over a 6-year period, the investigators indicate that patient care did not change meaningfully during that time, and patient management was similar in all 3 countries. Some patients were randomized twice into the trial, which is unusual. The investigators contend that this had no effect on the outcome. Platelets were stored for 5 days in Canada (as is done in the United States) or 7 days in Europe. There were no differences in results between 5-day and 7-day platelets.

This was a noninferiority trial with the primary end point being the proportion of patients who experienced World Health Organization grade 2 or greater bleeding. The primary end point was met with a bleeding rate of 54% in patients on the PRT arm and 51% on the control arm (P = .012). There were no differences in the percentage of days with bleeding, the highest grade of bleeding, and bleeding at different sites. This rate of grade 2 and also more serious grade 3 or 4 bleeding is similar to other randomized platelet transfusion trials in which bleeding was either the primary or secondary end point and other platelet transfusion clinical trials, indicating that these patients are similar to the general population of patients who receive platelet transfusions.

Almost 20% of patients in the treatment arm and 11.6% of patients in the control arm received off-protocol transfusions. Platelets hyperconcentrated or suspended in platelet additive solution were considered off protocol for the control arm. It is not clear whether these platelets would have a different clinical impact, so it is unfortunate that they were eliminated from further analysis.

In addition to intention to treat (ITT), a per-protocol (PP) analysis was carried out. For PP, transfusion episodes were excluded if the patient bled before the first study transfusion, did not receive any transfusions, or received >25% off-study transfusions. Unfortunately, this resulted in elimination of ~25% of transfusion episodes (425 PP vs 567 ITT) and resulted in a much smaller analysis. This lower-powered PP analysis did not show statistical significance for noninferiority.

A major change between the ITT and PP analyses was a large decrease in bleeding (from 51% to 44%) in the control group, whereas bleeding in the PRT group was essentially the same (54% vs 52%). Since the main difference between the ITT and PP analysis groups was the elimination of many transfusions from the control group, it appears that some patients with bleeding were removed, leading to inability to establish noninferiority in the PP analysis.

Three important secondary end points in this trial are the corrected count increment (CCI), number of platelet transfusions, and interval between transfusions. The lower CCI in the PRT arm is expected based on previous studies of PRT products and also radiolabeled platelet studies in normal research subjects. The lower CCI sometimes leads to a shorter interval between transfusion and more transfusions, but this is not always the situation in clinical practice.

As expected, these patients experienced quite a few adverse events. The proportions of AEs that could be imputed to the platelet product were 2.8% and 3.3% for the control and treatment arms, which were not different.

There are adequate in vitro and animal data to support lack of need to irradiate PRT platelets to prevent graft-versus-host disease (GVHD). This was left to local discretion. It does not appear that irradiation (or lack of) had a detrimental impact on the clinical effect of platelets. No cases of GVHD were reported.

It was suggested that this PRT technology might reduce alloimmunization. The rates reported here are remarkably low (3.8% for controls and 3.9% for PRT) and thus do not provide any helpful information regarding alloimmunization.

The overall message from this important study is that for prevention or treatment of bleeding, PRT platelets were not inferior to usual platelets in an ITT analysis. There were no differences in the percentage of days of bleeding or bleeding at different sites. Posttransfusion platelet counts were lower and the interval between transfusions was shorter as expected in the PRT group. No safety concerns were raised. When some patients were excluded, a PP analysis did not establish noninferiority. This raises the issue of the relative value of these 2 kinds of analysis. The important point is that failure to establish noninferiority does not establish superiority. In other words, while ITT establishes that the 2 platelet products have similar clinical effects, failure of statistical significance in the PP analysis does not establish that control platelets are better.

This report adds to the growing experience indicating that platelets subjected to PRT by both leading technologies are clinically effective in hemostasis. The authors have done all of us a great service by developing data that can help move this new paradigm for blood safety forward into wide clinical use.

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REFERENCES


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