reertoire integrity. They first established what diversity of T cells one might expect to find in any human subject by comparing the V and J subunit use of normal healthy controls as a sort of VJ use reference nomogram. They then compare the V and J use of T-cell clones in the CD8 Tem of recipients with CMV reactivation vs nonreactivation to the reference. They show that recipients with CMV reactivation have more pockets of V and J use with significantly fewer clones than expected. Thus, these patients appear to have more repertoire “holes” than expected, likely explained by CMV’s crooked actions in shaping T-cell immunity (see figure).

Transplant recipients with CMV reactivation also show statistically fewer native CD8 T cells, fewer CD8 memory T cells, and fewer CD4-naïve CD31+ recent thymic emigrants. These results suggest a potential defect in the repertoire needed to establish de novo adaptive immunity.

CMV-specific T cells are often dysfunctional in transplant patients with CMV reactivation. In addition, not all transplant patients who are CMV carriers reactivate. This leads to more questions. Are the repertoire defects caused by the CMV virus itself or other underlying susceptibilities in the genetic and cell architecture of the immune system, and if so, what are these factors? How can we contextualize potentially beneficial aspects of CMV reactivation like reduced relapse for patients with acute myeloid leukemia?

Although this study of relatively few patients is a landmark evaluation of T-cell repertoire health and CMV, there are some limitations. Many of the patients in the study had graft-versus-host disease and different immunosuppression doses. Both factors interact with CMV and affect T-cell repertoire. The authors looked at this and saw little effect on repertoire, but this needs further evaluation in more patients and transplant conditions.

The metric of repertoire “holes” is new, with some assumptions that have yet to be fully explored. We do not know if the reference VJ use “nomogram” employed uses the best human control comparator statistically. This study uses state-of-the-art sequencing depth, but this is still a very shallow level, many orders of magnitude below the T-cell population size in any human; therefore, although holes might exist at this sampling depth, does that really indicate a problem? What about T-cell subsets other than CD8 Tem, do they show the same patterns?

Despite these caveats, Sussemuth et al help advance how we interrogate the immune system after transplantation. Perhaps this takes us a step closer to using quantitative measurements of the adaptive immune system in clinical decision-making. As a result of studies like this, one day we may be answering a new type of question from our patients: “How’s my T-rep doing, doc?”

**Conflict-of-interest disclosure:** E.M. is a founder and holds stock options in GigaGen, Inc.

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**CLINICAL TRIALS AND OBSERVATIONS**

Comment on Burnett et al, page 3878

**Beyond the first glance: anthracyclines in AML**

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In this issue of *Blood*, Burnett et al present the results of United Kingdom (UK) National Cancer Research Council Acute Myeloid Leukemia 17 (NCRI AML17), a randomized comparison of daunorubicin (90 vs 60 mg/m²) in induction in 1206 patients with acute myeloid leukemia (AML), showing no benefit to the higher dosing.1

AML is a heterogeneous disorder with devastating consequences. It requires an aggressive treatment approach to control the disease and ultimately cure it. AML has been treated in a similar fashion for >40 years, with variations on the main theme. The mainstay of therapy has been an injected anthracycline (usually for 3 days) and continuously infused cytarabine for 7 days.2 The addition of other medications to this duet or dose intensification of cytarabine has not significantly improved outcomes.3-5

More recent studies have looked at the dose intensification of the anthracycline component to improve complete remission (CR) rates and overall survival (OS). The benefit of this method was first suggested by the large randomized trial from the Eastern Cooperative Oncology Group (ECOG), where high-dose daunorubicin of 90 mg/m² for 3 days was superior to the then standard of 45 mg/m² for 3 days.6 This improvement was noted in favorable and intermediate-risk disease. With further follow-up, the benefit has remained for these groups of patients and is now evident in unfavorable risk, including FLT3-ITD-positive disease.7

Other anthracyclines and dosing schedules of anthracyclines have recently been compared with daunorubicin. Most have demonstrated...
equivalent CR rates; however, no superiority in OS has been shown. Concerns about toxicity of high-dose (90 mg/m²) daunorubicin, the wide use of the 60-mg/m² dose as a newer “standard,” and similar remission rates of the 60-mg/m² dose led the UK NCRI AML Study Group to compare the 60- vs 90-mg/m² doses in induction in a prospective randomized trial.1

At first glance, the conclusions from the study were that there is no benefit to the higher daunorubicin dosing, nor was there a subgroup where the higher dose benefited patients. However, one needs to look beyond the simple calculation of anthracycline dose in the first induction and consider the total dose of anthracycline given over several courses. Compared with the ECOG, the Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON), and Korean trials, where a total of 270 mg/m² of daunorubicin was given to a majority of patients,4,9,10 in this trial, the total dose of daunorubicin was 330 mg/m² for the 60-mg/m² group and 420 mg/m² for the 90-mg/m² group. Therefore, the total anthracycline in the lower-dose arm was slightly higher than the high-dose arms in the 3 randomized trials. There were also differences in the dose schedules of anthracycline, where pharmacokinetics and pharmacodynamics could have impacted leukemic cell exposure and outcomes.

The UK NCRI AML17 trial brings to light that the true benefit of anthracycline in AML may be in a defined therapeutic window. A threshold level is required for benefit in CR rates, but further dose escalation of the drug may not significantly improve, and may even worsen, outcomes. CR rates were similar in both arms, with no difference in mortality at 30 days. However, in addition to the lack of benefit of the higher dose, the trial was stopped prematurely because of the higher 60-day mortality noted in the 90-mg/m² arm. Perhaps this study defines the point of diminishing returns where the benefit of increasing anthracycline begins to erode.

The final factor in this trial is the short follow-up of the UK NCRI AML17 study group. The other published comparative trials had a much longer follow-up. Moreover, with time, certain interactions have become more evident. For example, with an 80-month follow-up in the ECOG trial, FLT3-ITD-positive AML patients did benefit from a higher dose of anthracycline. In the UK NCRI AML17 trial, there was a trend to a higher-dose daunorubicin benefit in the FLT3-positive patients. Longer follow-up is required to determine whether it becomes significant.

The appealing factor here for the UK NCRI AML17 study is that the lower dose of daunorubicin may allow for a third targeting drug to be more easily inserted into the regimen to treat FLT3-positive, core binding factor-positive, or other subgroups of AML patients. The foundation of therapy for this disease has been available for 40 years. Collectively, we are optimizing the appropriate dosing in induction. In this and future studies, these variations on the theme need to be perused and not just given a quick glance.

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

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Comment on Goettel et al, page 3886

Daring to learn from humanized mice

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In this issue of Blood, Goettel and colleagues introduce a novel humanized mouse model of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, whereby mice lacking murine major histocompatibility complex class II (MHC II) and expressing human HLA-DR1 (NOD. Prkd-c<sup>-/-</sup>I2rg<sup>−/−</sup>H2-Ab1<sup>−/−</sup>; NSG<sup>−/+;</sup>) are reconstituted with hematopoietic stem cells (HSCs) from a patient with IPEX syndrome to generate a humanized model for primary immune deficiency presenting as fatal autoimmunity.1

“Humanized mice” allow the study of human immune cells in the context of human diseases for the evaluation of organ-specific pathologies for which human samples may not be available or accessible, and for the assessment of experimental approaches that may be harmful when performed in patients or human volunteers. Thus,
Beyond the first glance: anthracyclines in AML

Hugo F. Fernandez

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