

gene expression to predict the clinical response to tipifarnib and etoposide. *RASGRP1* is a guanine nucleotide exchange factor (GEF) that specifically activates *RAS*, and *Aprataxin* is a member of the histidine triad family of nucleotide hydrolases involved in the repair of DNA strand breaks.<sup>3</sup> The two-gene expression ratio (*RASGRP1/APTX*) was identified by analyzing gene expression profiles in bone marrow samples from older patients with previously untreated AML in a phase 2 study of tipifarnib. The results were validated in an independent set of samples from relapsed or refractory AML with negative predictive and positive predictive values of 92% and 28%, respectively (odds ratio of 4.4). The two-gene signature also predicted for improved overall survival (154 vs 56 days;  $P < .001$ ).<sup>3</sup> Here, Karp and colleagues confirmed the two-gene signature correlated with clinical response in a cohort of the elderly AML patients treated with tipifarnib and etoposide. Patients with a *RASGRP1/APTX* ratio of  $\geq 5.2$  had a CR rate of 78% compared with those with a ratio of  $< 5.2$  who had a CR rate of only 13%. The two-gene ratio did not correlate with outcome in other patients treated with conventional chemotherapy.<sup>1</sup>

The report by Karp et al contains important information in the search for the most effective way to use tipifarnib in the treatment of elderly AML. Technologies such as microarray gene expression assays may be paving the way to a better understanding of which genetic lesions are involved in the biology of AML and drug resistance, and thus possibly allowing for a more effective and perhaps personalized selection of appropriate therapies. Further work needs to be done to clarify whether the two-gene signature expression ratio has utility for other classes of FTIs and whether a qPCR assay can be applied in clinical practice.

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## ● ● ● TRANSPLANTATION

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# The Serenity Prayer for acute GVHD

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*Grant me the serenity to accept the things I cannot change, the courage to change the things I can, and the wisdom to know the difference.* (The Serenity Prayer; attributed to R. Niebuhr)

In this issue of *Blood*, Jagasia and colleagues identify new risk factors for acute GVHD (aGVHD) in a group of more than 5500 patients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).<sup>1</sup> By combining conditioning regimen intensity, preparative regimen, and stem cell source into 6 groups, investigators for the first time answer the prayer for factors that can be changed to decrease aGVHD risk.

**T**here have been numerous studies, including several from the CIBMTR and many individual transplantation centers, looking at demographic and transplantation factors associated with the risk of aGVHD.<sup>2-4</sup> These studies found risk factors that were demographic, which could not be altered. The most frequently identified factors included patient age, donor age, degree of match, cytomegalovirus status, female donor for a male patient, remission status, and performance status. Although the idea of risk-adapted aGVHD prophylaxis based on these factors was advanced, the reality of designing and testing such strategies has proven profoundly difficult. For an individual patient with multiple risk factors for aGVHD, often acceptance of the risk and prayer for a good outcome was the answer to the aGVHD hazard.

In the current study the investigators looked at the most common treatment categories in addition to individual factors. They evaluated 6 categories in matched sibling donor and unrelated donor transplantations: (1) myeloablative conditioning (MA) with

total body irradiation (TBI) + peripheral blood stem cells (PBSCs); (2) MA + TBI + bone marrow (BM); (3) MA + non-TBI + PBSCs; (4) MA + non-TBI + BM; (5) reduced-intensity conditioning (RIC) PBSCs; and (6) RIC + BM. Patients receiving sibling donor transplantations with MA + non-TBI + BM and RIC + PBSCs had much lower risks of significant GVHD than patients in other treatment categories. For patients with an unrelated donor, those receiving transplantations with MA + TBI + BM, MA + non-TBI + BM, RIC + BM, or RIC + PBSCs had lower risks of significant aGVHD. Tacrolimus plus methotrexate-based aGVHD prophylaxis was also associated with lower risk in both sibling and unrelated donor transplantations. This means that now for an individual patient with multiple demographic risk factors for GVHD, changing conditioning intensity, aGVHD prophylaxis, conditioning regimen, and/or graft source, in addition to prayer, should be considered in deciding on a treatment strategy.

This study by Jagasia et al also adds to a growing body of data published in the past year in this journal that suggests TBI is associated with increased risks for several late toxicities. Martires et al found an association with sclerotic chronic GVHD and patients receiving TBI in a RIC regimen.<sup>5</sup> Unfortunately, the preparative regimens in RIC transplants were not separately examined in the current study. The effects of TBI on growth and development (particularly in infants) and fertility have long been known. Sanders et al in a report on the late effects of transplantation in pediatric aplastic anemia patients also identified an increased risk for malignancy and chronic GVHD in patients receiving TBI (especially higher doses of TBI).<sup>6</sup> Oudin et al found that in adult survivors of pediatric leukemia, having an allogeneic transplantation with TBI increased the risk of development of metabolic syndrome compared with those who did not receive a transplant or had a non-TBI transplant.<sup>7</sup> TBI clearly has a proven role in transplantation, as recently reviewed by Hill-

Kayser et al,<sup>8</sup> but transplantation groups need the wisdom to use it in those who will benefit most. Likewise, new strategies to limit late toxicity to other organs by more specific targeting need to continue to be explored.<sup>9</sup>

Although the study by Jagasia and colleagues suffers from the usual concerns of registry-generated data, it is an answer to the prayers of many patients and transplantation centers. Hopefully, the CIBMTR and its investigators will continue to examine risk factors for other toxicities by looking at outcomes based on common treatment categories. It is always better to have treatment guided by data as well as prayer.

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