platelet glycoprotein Ibα–dependent localized amplification of coagulation by thrombin-mediated FXI activation fuels vascular inflammation, particularly in the context of neurohormonal activation involving angiotensin II–driven initiation of the TF pathway.[10] Targeting FXIa in this context also significantly reduces platelet procoagulant hyperreactivity, attenuates endothelial dysfunction, and prevents inflammatory vascular and renal damage.

Although clinical trial data on thrombosis prevention by FXI depletion or antibody-mediated inhibition of FXIa show promise, the clinical development of small-molecule protease inhibitors targeting the FXIa active site have so far produced inconclusive results. The efficacy of the different inhibitory strategies to affect the interactions of FXI in the kininogen-kinin system and interfere with platelet-localized activation of FXI in TF-initiated coagulation is currently being explored, but it remains unclear. Puy et al raise additional questions on how targeting FXIa and prevention of FXIa-PAI1 complex formation, which should also be achieved by small-molecule antagonists, can alter inflammatory signaling and potentially detrimental effects of excessive FXIa activation in cardiovascular diseases.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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https://doi.org/10.1182/blood.2024026283

TRANSPLANTATION

Comment on Kean et al, page 1834

Abatacept vs PT-Cy for GVHD prophylaxis

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In this issue of *Blood*, Kean et al demonstrated that graft-versus-host disease (GVHD) prophylaxis with abatacept plus a calcineurin inhibitor (CNI) plus methotrexate (MTX) improved overall survival (OS) in comparison with CNI/MTX or CNI/MTX plus antithymocyte globulin (ATG) after HLA-mismatched unrelated-donor (MMUD) hematopoietic cell transplantation (HCT).[1] Survival was comparable in patients receiving abatacept plus CNI/MTX or posttransplant cyclophosphamide (PT-Cy)-based GVHD prophylaxis.

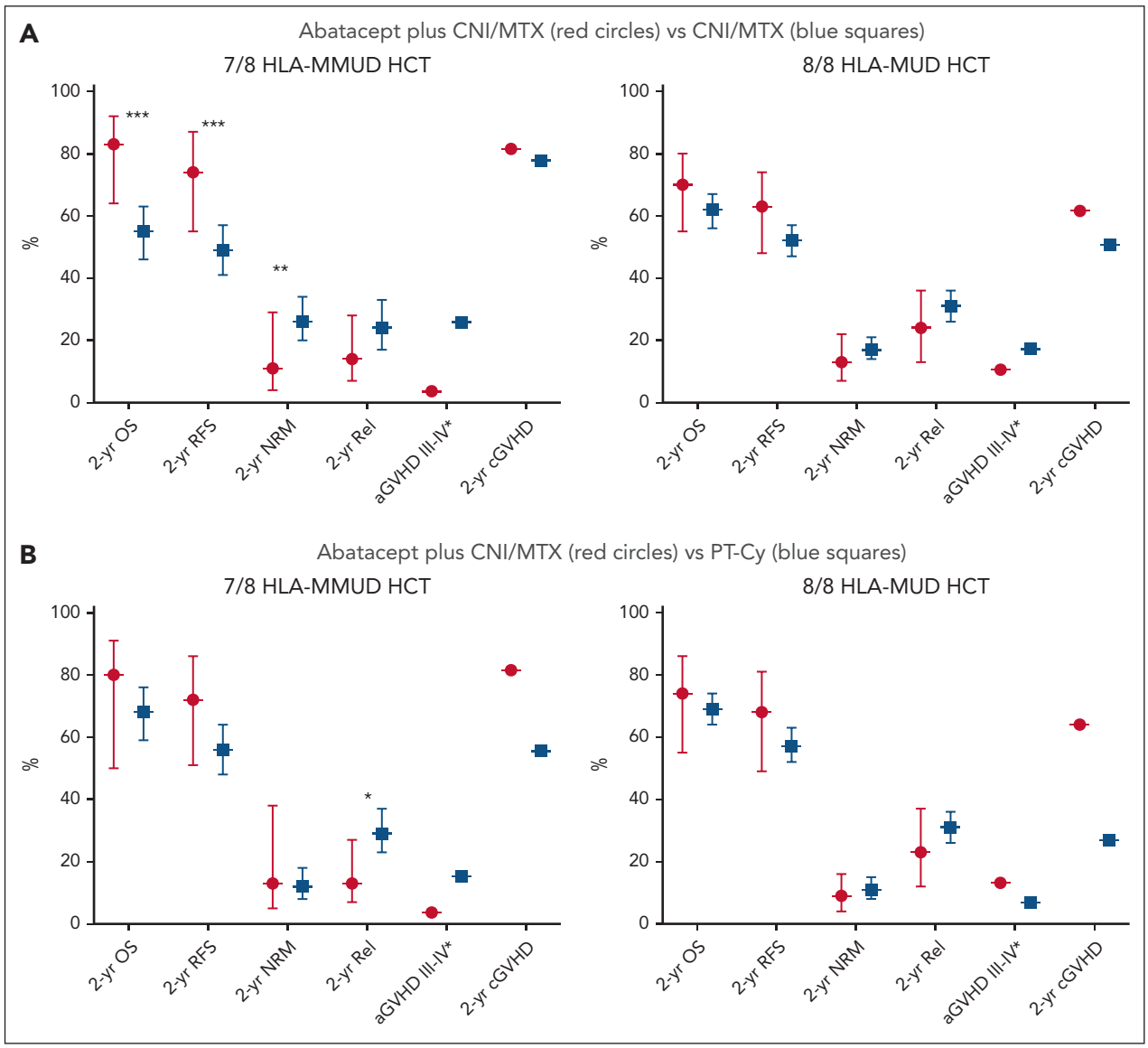
GVHD prevention is critical for the success of allogeneic HCT. CNI/MTX combination has been the standard for GVHD prophylaxis since the 1980s.[2] Unfortunately, this combination fails to prevent severe acute GVHD in 15% to 25% of patients receiving grafts from HLA-matched UD (8/8 MUD) and in more than 25% of those given grafts from 1 HLA-mismatched UD (7/8 MMUD).[1,3] Addition of ATG to CNI/MTX decreased the incidence of GVHD but without improving OS in MUD recipients[4] and largely failed to prevent severe acute GVHD in patients transplanted with MMUD.

Progress has been made recently in GVHD prophylaxis.[5] The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1703 phase 3 trial demonstrated that PT-Cy combined with tacrolimus plus mycophenolate mofetil improved GVHD-free, relapse-free survival (hazard ratio [HR] = 0.64, 95% confidence interval: 0.49-0.83) in comparison with tacrolimus plus MTX in patients undergoing HCT from either an HLA-matched related donor (n = 128), an 8/8 MUD (n = 288), or a 7/8 MMUD (n = 15) after reduced-intensity conditioning.[6] This was associated with a reduction in the incidences of grade III to IV acute (6.3% vs 14.7%) and chronic (21.9% vs 35.1% at 1 year) GVHD in the PT-Cy arm, without increasing disease progression (HR = 0.98). Supporting these data, a matched-pair analysis from the European Society for Blood and Marrow Transplantation (EBMT) in patients undergoing 9/10 MMUD HCT observed less grade III to IV acute GVHD (9% vs 19%, $P < .04$) and better relapse-free survival (RFS, 55% vs 34% at 2 years, $P < .05$) with PT-Cy than with ATG-based GVHD prophylaxis.[7]

Abatacept is a recombinant soluble cytotoxic T-lymphocyte-associated-4 (CTLA4) immunoglobulin G1 fusion protein that

modulates a costimulatory signal required for T-cell activation, a key step in GVHD pathogenesis. The drug was granted Food and Drug Administration approval for GVHD prophylaxis in MUD or MMUD recipients based on data from the ABA2 trial.[8] This trial compared GVHD prophylaxis with abatacept plus CNI/MTX vs CNI/MTX in 2 strata: patients with an 8/8 MUD were enrolled in a double-blind, placebo-controlled phase 2 study, and those with a 7/8 MMUD were enrolled in a single-arm study. The main findings of the AB2 trial were that, in the 8/8 MUD cohort, patients randomized in the abatacept arm tended to have a lower incidence of grade III to IV acute GVHD than those from the placebo arm (6.8% vs 14.8% at day 180, $P = .13$ at the statistical end point of the protocol), and in 7/8 MMUD, the 100-day cumulative incidence of grade III to IV acute GVHD was 2.3% in the study group vs 30.2% in Center for International Blood and Marrow Transplant Research (CIBMTR) controls.

In the Kean et al study reported in this issue of *Blood*, the authors performed a retrospective cohort analysis using CIBMTR data assessing abatacept plus CNI/MTX for GVHD prophylaxis not only in comparison with CNI/MTX alone, but also in comparison with CNI/MTX plus ATG and PT-Cy-based GVHD prophylaxis. The inclusion criteria included first HCT from an 8/8 MUD or a 7/8 MMUD between 2011 and 2018 in the United States as treatment for a hematological malignancy, 6 years of age or older, high-dose conditioning regimen (either total body irradiation/Cy, busulfan/Cy, busulfan/fludarabine, or fludarabine plus melphalan regimen) and GVHD prophylaxis with CNI/MTX (with or without ATG/abatacept) or PT-Cy (and no ATG). Comparisons were made separately in 7/8 MMUD and 8/8 MUD cohorts using weighted Cox proportional hazards models.



Impact of GVHD prophylaxis on transplantation outcomes. Transplantation outcomes in 7/8 HLA-MMUD and 8/8 MUD HCT weighted samples with abatacept plus a CNI plus MTX vs CNI/MTX alone (A) or abatacept plus CNI/MTX vs PT-Cy-based GVHD prophylaxis (B) in the study from Kean et al. Error lines show the 95% confidence intervals. *$P < .05$, **$P < .01$, and ***$P < .001$ for OS, RFS, NRM, and Rel comparisons between groups. NRM, nonrelapse mortality; Rel, relapse incidence; aGVHD III-IV, 180-day incidence of acute GVHD; cGVHD, chronic GVHD.

In the 7/8 MMUD cohort, patients in the abatacept plus CNI/MTX group had significantly higher 2-year OS (83% vs 55%, $P = .0036$) and RFS (74% vs 49%, $P = .0098$) than those from the CNI/MTX control group (see figure panel A). This was mainly due to a lower incidence of nonrelapse mortality in the abatacept group. Similarly, patients in the abatacept plus CNI/MTX group had higher 2-year OS (83% vs 46%, $P = .0005$) and RFS (77% vs 35%, $P = .0002$) than patients in the CNI/MTX plus ATG group. In contrast, 2-year OS (80% vs 68%, $P = .23$) and RFS (72% vs 56%, $P = .11$) were comparable in patients in the abatacept plus CNI/MTX group and patients in the PT-Cy group. Of note, however, relapse incidence was lower in the abatacept plus CNI/MTX group than in the PT-Cy group (13% vs 29%, $P = .025$). Regarding GVHD, although the 180-day incidence of grade III to IV acute GVHD was lower in patients in the abatacept plus CNI/MTX (3.7%) group than in patients in the CNI/MTX (25.9%), CNI/MTX plus ATG (27.8%), and PT-Cy (15.4%) groups, the 2-year incidence of chronic GVHD was markedly higher in the abatacept plus CNI/MTX group than in the PT-Cy group (81.5% vs 55.6%).

The benefit for abatacept appeared less strong in the 8/8 MUD cohort in which OS and RFS were not significantly different in patients in the abatacept plus CNI/MTX group than in those from the 3 control groups (see figure panel B). Regarding GVHD, the 180-day incidence of grade III to IV acute GVHD was lower in the abatacept plus CNI/MTX (10.6%) and the PT-Cy (6.8%) groups than in CNI/MTX (17.3%) group. However, 2-year incidence of chronic GVHD was lower in PT-Cy (27%) and CNI/MTX plus ATG (38%) groups than in abatacept plus CNI/MTX group (61%).

The study by Kean et al is important because it is the first to compare outcomes between abatacept plus CNI/MTX vs PT-Cy-based GVHD prophylaxis. Results show at least comparable OS and RFS with abatacept and PT-Cy-based GVHD prophylaxis, which could set the basis of a future large prospective phase 3 trial. Interestingly, among 7/8 MMUD recipients, relapse incidence was significantly lower in abatacept than in patients in the PT-Cy group. This might suggest that PT-Cy could impair graft-versus-leukemia effects in this setting, although this was not observed in the BMT CTN 1703 phase 3 trial.[6] Since data on dose and brand of ATG are not captured in the CIBMTR database, the comparisons between ATG and abatacept groups reported here should be taken with some caution. Finally, one potential matter of concern is the high incidence of chronic GVHD observed in patients treated with abatacept plus CNI/MTX. Results of the ABA3 (NCT04380740) trial randomizing patients undergoing 7/8 MMUD transplantation to receive 4 additional doses of abatacept beyond day +28 through day +150 are particularly awaited to determine whether this extended schedule reduces chronic GVHD without increasing relapse.

Conflict-of-interest disclosure: F.B. declares no competing financial interests. ■

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https://doi.org/10.1182/blood.2024026116