THE END (AND BEGINNING) OF AN ERA FOR GRAFT-VERSUS-HOST DISEASE

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Once, when I was a resident, a wise (autologous transplant) attending hematologist said, "There are fates worse than death, and chronic graft-versus-host disease is one of them." In a recent multisite study, 2-year survivors who underwent allogeneic stem cell transplant (allo-SCT) for acute myeloid leukemia (AML) had a 3.8-fold higher risk of severe/life-threatening conditions than their nearest-age siblings.[1] Two-thirds of allo-SCT survivors had a history of chronic graft-versus-host disease (cGVHD). Survivors with cGVHD were ≥2 times more likely to report poor general health, activity limitation, pain, and anxiety or fears. than survivors without cGVHD.

For the past 40 years, the standard of care to prevent graft-versus-host disease (GVHD) has remained a calcineurin inhibitor plus methotrexate. Approximately 30% to 50% of patients who receive allo-SCT develop acute GVHD, and 14% develop severe acute GVHD.[2] Chronic GVHD occurs in 30% to 70% of patients who receive allo-SCT.[3] Multiple randomized studies designed to reduce the incidence and/or severity of GVHD met with disappointing results owing to increased risk of relapse, unacceptable toxicity, and/or lack of efficacy. A late-breaking abstract presented at the American Society of Hematology (ASH) Annual Meeting by Shernan Holtan, MD, Associate Professor of Medicine at the University of Minnesota in Minneapolis was applauded for ushering in a new standard of care for GVHD prophylaxis in patients receiving reduced-intensity conditioning allo-SCT.

Recipients of allogeneic stem cell transplant (allo-SCT) may receive stem cells from the following types of donors:

- Matched sibling donors
- Matched unrelated donors
- Cord blood
- Haploidentical donors (usually a parent or a child)

Allo-SCT is a curative treatment option most frequently used to manage patients with

- Acute myeloid leukemia
- Myelodysplastic syndrome
- Acute lymphoblastic leukemia
- Chronic lymphocytic leukemia
- Chronic myelocytic leukemia
- Non-Hodgkin lymphoma
- Hodgkin lymphoma

The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 1703 study ("A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation") enrolled patients with hematologic malignancies who received reduced intensity conditioning followed by peripheral blood allo-SCT.[4] The majority of patients had AML or myelodysplastic syndrome and had an 8/8 matched unrelated donor. Almost one-fourth of patients received planned posttransplant maintenance therapy to prevent disease relapse. Patients were randomly assigned to receive GVHD prophylaxis with tacrolimus and intravenous methotrexate, as the standard of care arm, or with tacrolimus, mycophenolate mofetil, and posttransplant cyclophosphamide. Investigators found a reduction in GVHD-free, relapse-free survival (GRFS), from 53% to 35% at 1 year ($P < 0.001$), driven by a 50% reduction in grade III to IV acute GVHD (14.7%-6.3%) and cGVHD requiring immunosuppression (25%-12.5%). No difference in relapse, progression, or overall survival was observed.

BMT CTN 1703 was a remarkable study in multiple ways. It completed enrollment a year ahead of schedule, despite beginning enrollment 6 months before the COVID-19 worldwide pandemic. The study evaluated a drug that was approved for medical use in the United States in 1959 and was funded without industry support. It was the first prospective, phase 3 study to use GRFS[5] as a primary endpoint. Perhaps most importantly, it demonstrated a reduction in GRFS without a clinically meaningful difference in severe toxicity (myelosuppression, graft failure, grade ≥3 infection). Dr. Holtan's colleagues at the University of Minnesota presented a phase 2 study of patients receiving posttransplant cyclophosphamide/tacrolimus/mycophenolate mofetil after myeloablative conditioning allo-SCT at the ASH Annual Meeting.[6] This study also reported a markedly low rate of grade II to IV acute GVHD (16%) and cGVHD requiring immunosuppression (4%). In a conversation with Dr Holtan (December 2022), she noted that the study did include pediatric patients and some patients with bone marrow grafts, which may explain why the rate of cGVHD appears somewhat lower than in BMT CTN 1703. Dr. Holtan indicated their center has been methotrexate-free since 2018 and "it's a totally different practice now" because so many fewer patients have cGVHD.

In 2021, the FDA approved abatacept (ORENCIA®) in combination with a calcineurin inhibitor and methotrexate to prevent acute GVHD in adult and pediatric patients aged ≥2 years undergoing hematopoietic SCT from a matched or 1 allele-mismatched unrelated donor.[7] This is the only FDA-approved drug for acute GVHD prophylaxis. Notably, this regimen did not impact cGVHD, with 1-year cGVHD cumulative incidence of 51.9% in 8/8 matched unrelated donor recipients, nor did it improve nonrelapse mortality or overall survival.

Decades of research are finally benefiting patients receiving allo-SCT. Ibrutinib, a Bruton's tyrosine kinase inhibitor, was approved by the FDA in 2017 for adult patients with cGVHD after failure of 1 or more treatments based on a phase 1b/2, open-label, multicenter study.[8] In 2022, the use of ibrutinib was also approved for pediatric patients aged ≥1 year.[9] Ruxolitinib, a JAK1/2 inhibitor, was approved in 2019 for steroid-refractory acute GVHD in adult and pediatric patients aged ≥12 years, based on a multicenter, randomized, open-label phase 3 trial for steroid-refractory acute GVHD.[10] Ruxolitinib was FDA-approved in 2021 for cGVHD, based on the REACH-3 trial, a randomized, open-label, multicenter clinical trial of ruxolitinib compared with best available therapy for corticosteroid-refractory cGVHD after allo-SCT.[11] In 2021, based on results from the phase 2, randomized, multicenter ROCKstar trial, the FDA approved belumosudil, a selective ROCK2 inhibitor, for adult and pediatric patients aged ≥12 years with cGVHD after failure of ≥2 prior lines of systemic therapy.[12]

Conditioning chemotherapy is administered before stem cell infusion, both to suppress the patients' immune system to prevent graft rejection and graft-versus-host disease and to kill cancer cells. Alkylating agents, purine analogs, and radiation are the most often used therapies in reduced intensity conditioning regimens. Reduced intensity conditioning regimens were developed to allow older patients and those with more comorbidities to tolerate the regimen and rely more heavily on the graft-versus-leukemia effect to cure the cancer than a myeloablative regimen.

Dr. Holtan views the future as "continuing to refine conditioning and GVHD prophylaxis regimens to try to keep it all within a short period of time." She noted, "We have to really take into consideration, as much as we can, minimizing health care burdens overall and trying to get the therapeutic benefit done quickly, as much as possible."

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