Immunosuppression with posttransplant cyclophosphamide for allogeneic hematopoietic cell transplantation

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TITLE	Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplant cyclophosphamide.
AUTHORS	Luznik L, Jalla S, Engstrom LW, Iannone R, Fuchs EJ.
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Allogeneic hematopoietic cell transplant for hematologic malignancies can be curative but until about two decades ago was limited to those with a human leukocyte antigen (HLA)-matched sibling or an HLA-matched or mismatched adult donor. Increased access to transplantation in the early 2000s was in part brought about by transplanting bone marrow from a haploidentical relative. The landmark publication from the Johns Hopkins University School of Medicine in 2001 showed that in mouse models a combination of fludarabine, total body irradiation and cyclophosphamide is sufficient conditioning for engraftment with $10x10^6$ major histocompatibility complex (MHC)-incompatible bone marrow cells and that fludarabine can be substituted for T-cell specific antibodies.[1] Posttransplant cyclophosphamide decreased the incidence and severity of acute graft-*versus*-host disease (GvHD) after transplantation of MHC-incompatible bone marrow cells and this was not associated with global immunosuppression, which is consistent with cyclophosphamide's selective toxicity to T cells activated by antigen recognition (i.e., selective toxicity to proliferating alloreactive T cells instead of non-proliferating, non-alloreactive T cells). Reducing the dose of total body irradiation to 200 cGy further minimized the risk of GvHD. The safety and efficacy of the nonmyeloablative conditioning and high-dose posttransplant cyclophosphamide at preventing graft rejection and GvHD after transplantation of bone marrow from a haploidentical relative were studied in patients with advanced hematologic malignancies at the Johns Hopkins and Fred Hutchinson Cancer Research Center (Figure 1).[2] Sixty-eight consecutive patients for whom standard allogeneic or autologous transplantation was unavailable or inappropriate were enrolled between 1999 and 2006. The trial[2] concluded that posttransplant immunosuppression with high-dose cyclophosphamide, tacrolimus and mycophenolate mofetil was associated with low incidences of fatal graft rejection, severe acute GvHD and extensive chronic GvHD, and a suggestion of effective clinical immune reconstitution as evidenced by low rates of severe opportunistic infections. Recurrent disease was the major cause of treatment failure. Nevertheless, the 2-year survival was 36%.

During the same period, at the University of Minnesota John Wagner led a phase II trial of transplantation of two HLA-mismatched unrelated umbilical cord blood units after a nonmyeloablative conditioning regimen and posttransplant immunosuppression with cyclosporine and mycophenolate mofetil, which paved the way for another alternative source of donor cells. In 2006, the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) in the USA conducted two parallel phase II trials. Using identical inclusion and exclusion criteria and a common study design, the trials evaluated the effectiveness of haploidentical donor and double umbilical cord blood transplantation for adults with high-risk leukemia or lymphoma who lacked a suitable matched related donor. These multicenter trials confirmed that transplantation of both haploidentical donor grafts and double umbilical cord blood was effective and set the stage for a multicenter randomized trial to assess the relative efficacy of these two alternative sources of donor cells.[3] Unlike the timely accrual to the phase II parallel trials, the randomized trial failed to accrue as planned and was closed to further entry of patients by its Data Safety Monitoring Board after having

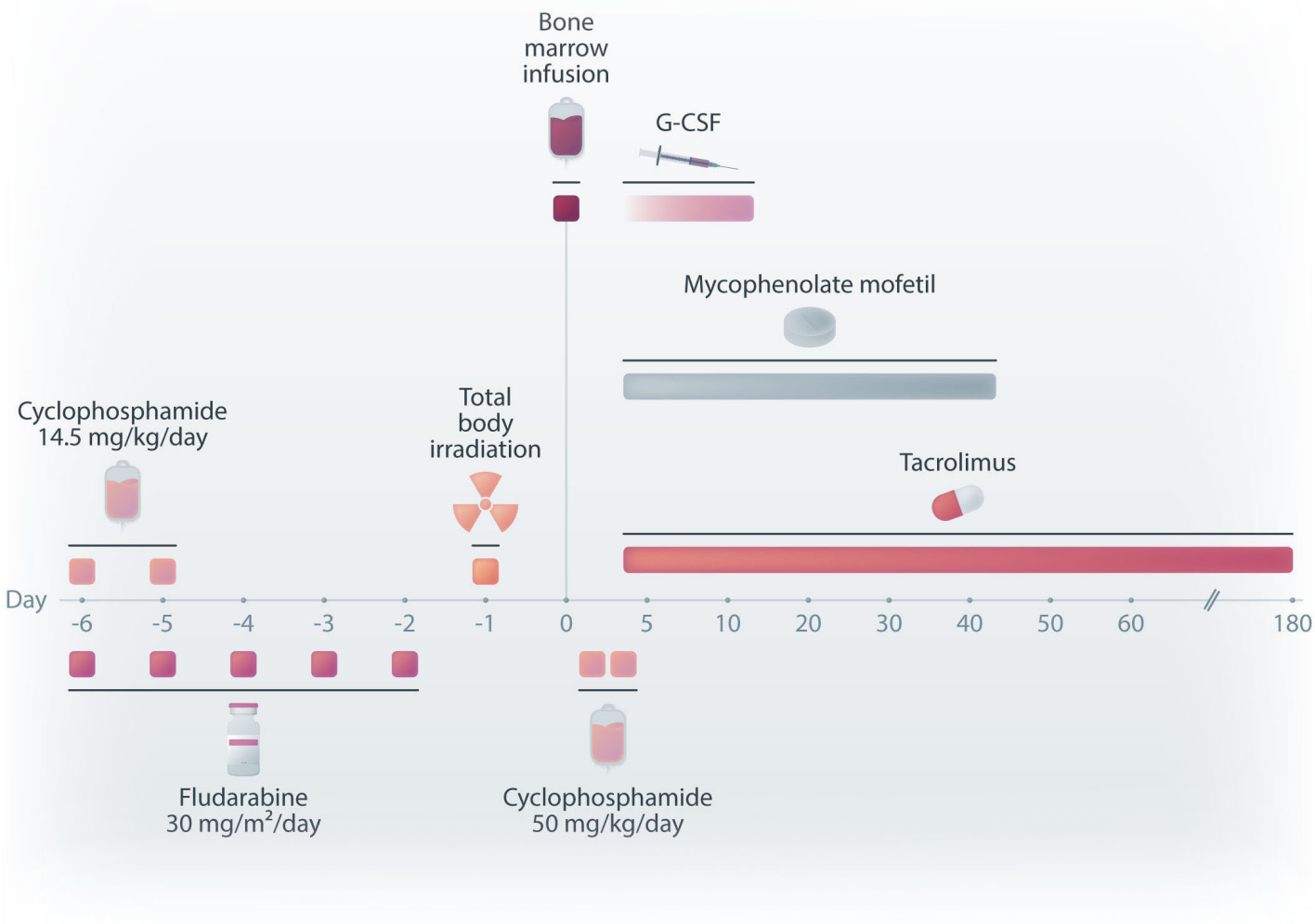

Figure 1. Nonmyeloablative haploidentical bone marrow transplant conditioning and immunosuppressive regimens. G-CSF: granulocyte colony-stimulating factor. *Adapted with permission from Blood. 2021;137(3):420-428.*

included 90% of the planned accrual. This trial concluded that both alternative sources of donor cells extend access to transplantation. Lower non-relapse mortality and higher 2-year survival favored haploidentical transplantation.[3] Consequently, there are substantially more haploidentical transplants and very few umbilical cord blood transplants performed in the USA now.

Control of GvHD is one of the most important determinants of a successful outcome after allogeneic hematopoietic cell transplantation and, for approximately four decades, a calcineurin inhibitor with methotrexate became the standard regimen for GvHD prevention. Immunosuppression with posttransplant high-dose cyclophosphamide, tacrolimus and mycophenolate mofetil compared to tacrolimus and methotrexate was recently studied in a randomized trial for adults with hematologic malignancy.[4] Patients underwent transplantation from an HLA-matched sibling or HLA-matched or mismatched unrelated donor. This trial concluded that the rate of GvHD-free, relapse-free survival was higher after immunosuppression with posttransplant high-dose cyclophosphamide, tacrolimus and mycophenolate mofetil and extends the application of this approach to GvHD prevention. In conclusion, immunosuppression with posttransplant, high-dose cyclophosphamide, tacrolimus and mycophenolate mofetil increased access to transplantation and has set a new standard for GvHD prevention after hematopoietic cell transplantation.

Disclosures

No conflicts of interest to disclose.

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