Allogeneic Transplantation for Myelofibrosis with Novel Graft-versus-Host Disease Prophylaxis

Leonid Volodin Karen K. Ballen

Division of Hematology/Oncology, University of Virginia Cancer Center, Charlottesville, VA, USA

Allogeneic hematopoietic cell transplantation (HCT) for patients with myelofibrosis (MF) has been associated with high rates of non-relapse mortality (NRM), poor graft function, graft-versus-host disease (GVHD), and disease relapse. Strategies to reduce relapse rate, improve graft function, and mitigate toxicity are needed to improve outcomes. The use of post-transplant cyclophosphamide (PTCy) for GVHD prophylaxis is one strategy that has been used in matched- and mismatched-donor transplants to reduce the incidence of GVHD, especially chronic GVHD. Ruxolitinib is an inhibitor of a JAK-STAT pathway and has efficacy in the treatment of acute and chronic GVHD as well as in the treatment of MF, making it an attractive agent to mitigate relapse and risk of GVHD at the same time.

In this issue of *Acta Haematologica*, Morozova et al. [1] report a single-center prospective study of allogeneic transplant for MF patients in Russia, employing a reduced-intensity conditioning (RIC) regimen with peripheral blood stem cell graft use, and studying a combination PTCy and ruxolitinib primary GVHD prophylaxis. The authors enrolled 20 patients, using 14 matched donors and 6 mismatched donors (4 haploidentical and 2 mismatched unrelated donors). The authors documented an incidence of acute and chronic GVHD comparable to other recently reported trials. They also observed an acceptable NRM of 15% and only one relapse out of 17 surviving patients. This study is one of the few studying a PTCy-based approach in MF, demonstrating

feasibility of the combination of PTCy/ruxolitinib in this setting, with an estimated 2-year survival of 85%. The authors did, however, observe a severe poor graft function (SPGF) in 11 of 18 patients, 5 of whom required either a CD34+ cell boost or a donor lymphocyte infusion from the original donor to improve graft function. There was also one case of primary graft failure requiring a second HCT. Of note, the study included 6 patients who received transplants from mismatched donors, generally considered at higher risk of GVHD and NRM. The regimen used the total dose of 10 mg/kg of oral busulfan in combination with fludarabine, which most consider myeloablative, thereby providing stronger protection against relapse, with possible toxicity implications. A limitation is that most centers have moved to intravenous busulfan with pharmacokinetic monitoring to reduce toxicity. The study team actively monitored for SPGF as defined by blood counts, and intervened as necessary to improve graft function post-transplant. Seven of 20 patients also underwent splenectomy prior to HCT.

A solo PTCy has been successfully used as a GVHD prophylaxis in patients with other hematological malignancies, who received bone marrow grafts from matched related and unrelated donors using a myeloablative Bu/Flu conditioning regimen [2]; however, the same approach was associated with a higher incidence of GVHD and a NRM of 36% at 2 years, when peripheral blood stem cell grafts were used [3]. The Blood and Marrow Trans-

plant Clinical Trials Network study 1203 [4] further explored the use of a peripheral graft in a matched-donor setting, employing a reduced-intensity conditioning regimen, and using a traditional combination of tacrolimus and mycophenolate mofetil in addition to PTCy for GVHD prophylaxis. The study reported positive outcomes, namely low grade 3–4 acute GVHD of 2%, a lower chronic GVHD rate of 28%, and low NRM of 11%. None of the above studies, however, included patients with MF.

Transplants aimed at MF patients have historically noted a higher incidence treatment-related mortality of 32–48% at 3 years, relapse of 23–28%, and lower survival rates of 33–44% based on the Center for Blood and Marrow Transplant Research database, looking at 287 transplants done in the United States between 1989 and 2002 [5]. More recent data from a single-institution cohort suggest that better outcomes are achievable [6], with a 2-year survival of 81.1%, NRM of 16.2%, low relapse rates, and a 7% graft failure rate. Interestingly, this study used ruxolitinib pre-transplant for treatment of MF, and as needed post-transplant for GVHD, graft rejection, or persistent MF. A European study of the same backbone Bu/Flu chemotherapy as the current study, but using a conventional GVHD prophylaxis in a MF population between 2002 and 2007 [7], noted estimated 5-year survival rates of 67% and an acceptable NRM of 16%, as well as a relapse rate of 22% at 3 years. The primary graft failure rate was at 2%. This study used cyclosporine A and a short course of methotrexate for GVHD prophylaxis, adding ATG for mismatched donors. Of note, mismatched donors in this study had worse survival with NRM of 38% compared to 12% for matched-donor transplants.

Despite its limitations, the current study provides useful information that can serve as a stepping-stone in the development of further effective therapies for MF. A combination of reduced toxicity Bu/Flu regimen and PTCy, as well as subsequent JAK inhibition provides a higher total dose of chemotherapy and targeted therapy that the patient is exposed to, allowing for a more effective cyto-reduction, which can translate into a lower relapse rate. Similarly, using JAK-STAT inhibition and PTCy allows for an adequate GVHD prevention comparable to historic numbers. To further reduce toxicity, this approach can be restricted to matched related or matched unrelated donors, which would further reduce the incidence of acute and chronic GVHD. Ruxolitinib has a known hematological toxicity of cytopenias, and may in part be contributing to the high SPGF noted in this study. Strategies to mitigate this, such as proactive CD34+ cell boost, ruxolitinib dose reduction, or substitution with itacitinib, an investigational preferential JAK1 inhibitor, should be considered to further improve outcomes and quality of life in MF patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Leonid Volodin: writing and editing. Karen Ballen: expert opinion, writing, and editing.

References

- Morozova EV, Barabanshikova MV, Moiseev IS, Shakirova AI, Barhatov IM, Ushal IE, et al. A prospective pilot study of graft-versus-host disease prophylaxis with posttransplantation cyclophosphamide and ruxolitinib in patients with myelofibrosis. *Acta Haematol*. 2020. <https://doi.org/10.1159/000506758>.
- Kanakry CG, O'Donnell PV, Furlong T, de Lima MJ, Wei W, Medeot M, et al. Multi-institutional study of post-transplantation cyclophosphamide as single-agent graft-versus-host disease prophylaxis after allogeneic bone marrow transplantation using myeloablative busulfan and fludarabine conditioning. *J Clin Oncol*. 2014 Nov;32(31):3497–505.
- Holtick U, Chemnitz JM, Shimabukuro-Vornhagen A, Theurich S, Chakupurakal G, Krause A, et al. OCTET-CY: a phase II study to investigate the efficacy of post-transplant cyclophosphamide as sole graft-versus-host prophylaxis after allogeneic peripheral blood stem cell transplantation. *Eur J Haematol*. 2016 Jan;96(1):27–35.
- Bolaños-Meade J, Reshef R, Fraser R, Fei M, Abhyankar S, Al-Kadhimi Z, et al. Three prophylaxis regimens (tacrolimus, mycophenolate mofetil, and cyclophosphamide; tacrolimus, methotrexate, and bortezomib; or tacrolimus, methotrexate, and maraviroc) versus tacrolimus and methotrexate for prevention of graft-versus-host disease with haemopoietic cell transplantation with reduced-intensity conditioning: a randomised phase 2 trial with a non-randomised contemporaneous control group (BMT CTN 1203). *Lancet Haematol*. 2019 Mar;6(3):e132–43.
- Ballen KK, Shrestha S, Sobocinski KA, Zhang MJ, Bashey A, Bolwell BJ, et al. Outcome of transplantation for myelofibrosis. *Biol Blood Marrow Transplant*. 2010 Mar;16(3):358–67.
- Chhabra S, Narra RK, Wu R, Szabo A, George G, Michaelis LC, et al. Fludarabine/Busulfan Conditioning-Based Allogeneic Hematopoietic Cell Transplantation for Myelofibrosis: Role of Ruxolitinib in Improving Survival Outcomes. *Biol Blood Marrow Transplant*. 2020 Jan 23. pii: S1083-8791(20)30021-5. doi: <https://doi.org/10.1016/j.bbmt.2020.01.010>.
- Kröger N, Holler E, Kobbe G, Bornhäuser M, Schwerdtfeger R, Baurmann H, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2009 Dec;114(26):5264–70.