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Letters to the Editor

Dual T Cell Depletion with Anti-Thymocyte Globulin and Post-Transplant Cyclophosphamide Results in Low Rates of Cytokine Release Syndrome in Peripheral Blood Haplo-Hematopoietic Stem Cell Transplantation

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To the Editor:

Increasing experience with haplo-hematopoietic stem cell transplantation (HSCT) has brought attention to unique toxicities that may be less common with other modalities of transplantation such as cytokine release syndrome (CRS) [1-3]. We read with interest the study by Imus et al. [4]. The authors report a large retrospective experience on CRS after haplo-HSCT using peripheral blood (PB) allografts and post-transplant cyclophosphamide (PTCy) for graft-versus-host disease (GVHD) prophylaxis [4].

The authors report very high rates of CRS documented in 177 (90%) recipients. Severe CRS occurred in 17%, and 50% of them died in the first 6 months after transplantation [4]. Post-haplo-HSCT CRS is thought to be secondary to an intense and rapid proliferation of alloreactive T cells due to major HLA mismatch and a secondary elevation of circulating proinflammatory cytokines [5]. Clinical manifestations of CRS frequently appear in the immediate postinfusion period, whereas fever is the most common symptom encountered [4]. Because noninfectious fever and hypotension are frequent symptoms after stem cell infusion in haplo-HSCT [5,6], the diagnosis of CRS can be challenging. Although no confirmatory biomarkers exist, elevated C-reactive protein and IL-6 suggest a mechanism consistent with CRS in other settings [7].

At Princess Margaret Cancer Center, a Reduced Intensity Conditioning regimen consisting of fludarabine (30 mg/m^2/d $\times$ 4 days from days -5 to -2), busulfan (3.2 mg/kg/d $\times$ 2 days from days -3 to -2), and 200 cy of total body irradiation became the institutional standard of care for PB haplo-HSCT in August 2016. A novel combination using rabbit anti-thymocyte globulin (ATG) (total dose 4.5 mg/kg from day -3 to -1) combined with PTCy (50 mg/kg/day on days +3 and +4) and cyclosporine (from day +5) was used for GVHD prophylaxis. The efficacy of this combination for controlling GVHD has been previously reported by Viswabandya et al. [8,9]. To compare our results with those reported by Imus et al. [4], we performed a retrospective subanalysis of 51 patients who underwent haplo-HSCT for hematologic malignancies with the described protocol between August 2016 and May 2018. Median age was 56 years (range, 22 to 73 years). Indications for transplant were as follows: 28 (54.9%) of the recipients had acute myeloid leukemia, 8 (15.7%) had myelodysplastic syndrome, 5 (9.8%) had acute lymphoblastic leukemia, 3 (5.9%) had myeloproliferative neoplasms, 6 (11.8%) had lymphoma or chronic lymphocytic leukemia, and 1 had blastic plasmacytoid dendritic cell neoplasm (BPDCN). All recipients diagnosed with acute myeloid leukemia, acute lymphoblastic leukemia, and BPDCN were in complete remission before haplo-HSCT. Seven (13.7%) recipients had a Karnofsky performance status $\leq$80% and 24 (47%) an Hematopoietic Cell Transplant - Comorbidity Index score $\geq$3.

Postinfusion CRS was identified in 5 (10%) recipients and was grades 1 to 2 in all cases. Eleven (21.5%) recipients developed fever during the first 24 hours postinfusion without absence of hemodynamic instability or infection. However, no CRS was reported on clinical records, and these events were instead considered postinfusion fevers, not otherwise specified. The retrospective nature of our subanalysis and of the work by Imus et al. [4] is an important limitation. If we consider these patients as having grade 1 CRS, the incidence would increase to 31.3%. All our patients responded to conservative management alone and underwent rapid resolution of fever and other

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symptoms shortly after PTCy administration. No patients required intensive care unit assessment or admission due to CRS. Graft failure rate was 15.6% (76% secondary). The cumulative incidence of acute GVHD grade II-IV, and grade III-IV at day +100 was 21.6% and 7.8%, respectively. The cumulative incidence moderate/severe chronic GVHD at 1 year was 17.6%. With a median follow-up of 14.7 months, 27 (52.9%) recipients died and 11 (21.6%) relapsed. Main causes of death were relapse (15.7%), infection (21.6%), and graft failure (9.8%). One-year overall survival, relapse-free survival, nonrelapse mortality, and GVHD-free/relapse-free survival were 58.8%, 52.9%, 31.4%, and 35.3%, respectively. Given the high rates of infection and secondary graft failure, the conditioning regimen was refined by reducing the dose of ATG to 2 mg/kg. With this change, we aim to ameliorate infectious complications while preserving the GVHD-preventing properties of this regimen and improve donor T cell recovery, leading to more robust engraftment. These changes were instituted in May 2018, and the data are under analysis. In addition, we are now using pre-emptive rituximab in patients with asymptomatic Epstein-Barr virus reactivation at titers $>3 \times 10^6$/mL with excellent results (unpublished data). The protocol continues to undergo refinement to further limit complications and reduce nonrelapse mortality.

The use of dual T cell depletion with ATG and PTCy for GVHD prophylaxis in haplo-HSCT with PB allografts was associated with a much lower incidence of CRS overall and an absence of severe CRS. We hypothesize that this effect may be explained by the residual effect of ATG, leading to a reduction in the number of alloreactive T cells present in unmanipulated PB allografts, thereby resulting in a lower incidence of infusion reactions and CRS. In addition, low rates of clinically relevant acute and chronic GVHD were documented in our subanalysis, supporting the efficacy of targeting alloreactive T cell lymphocytes through dual-modality T cell depletion when PB allografts are used for haplo-HSCT.

Uncontrolled CRS, particularly if unresponsive to PTCy administration, is a pressing concern in haplo-HSCT. Tocilizumab has been used to treat CRS in this setting, but there are no reports of prophylactic approaches [7]. We hypothesize that reducing the incidence or mitigating the severity of CRS may be possible by using T cell modulation strategies such as ATG. Bone marrow is a safe and reliable stem cell source and is associated with very low rates of CRS in comparison to PB [10] but may not be feasible in all cases due to donor variables. Although we recognize that bone marrow may be the preferred graft source in some centers, the use of peripheral blood stem cells and resultant concerns with regard to increased risk of chronic GVHD may be mitigated by using a dual T cell depletion strategy such as ours. Evaluating the incidence and severity of CRS in the context of haplo-HSCT across multiple centers and a variety of conditioning regimens, GVHD prophylaxis strategies and graft sources will provide much-needed insight into this complication. Prospective studies assessing cytokine levels and their patterns in the peritransplant setting may identify patients at higher risk where prophylactic strategies could be more useful.

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