American Journal of Leukemia Research

Case Report
Published: 24 May, 2018

Complete Resolution of Steroid-Refractory Acute Graft-Versus-Host Disease using Alemtuzumab after Haplo-Identical Transplant

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Abstract

Acute Graft versus Host Disease (aGvHD) is a serious complication after allogeneic Hematopoietic Stem Cell Transplant (allo-SCT). Haploidentical-SCT (haplo-SCT) is increasingly utilized as it offers reliable and expeditious source for stem cells. However the incidence of aGvHD and high non-relapse mortality after haplo-SCT is a major concern. Glucocorticoids are still the gold standard therapy for aGvHD, but up to 50% of patients with acute gastro-intestinal and liver aGvHD are steroid refractory and the outcome of such steroid refractory patients is universally poor. There are no standard of care guidelines for steroid-refractory aGVHD and various modalities have been tried. We report a patient with B-ALL who developed steroid-refractory grade IV aGvHD of gut and liver after haplo-SCT, which was successfully treated with alemtuzumab. To our knowledge, this is first case report of successful use of alemtuzumab for treatment of steroid refractory aGvHD in haplo-SCT.

Keywords: Haploidentical-stem cell transplant; GVHD; Alemtuzumab

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Received Date: *11 Apr 2018*
Accepted Date: *17 May 2018*
Published Date: *24 May 2018*

Citation:
Sasapu A, Veeraputhiran MK, Motwani P, Burgess M, Kothari A, Rico JC, et al. Complete Resolution of Steroid-Refractory Acute Graft-Versus-Host Disease using Alemtuzumab after Haplo-Identical Transplant. Am J Leuk Res. 2018; 2(1): 1011.

Case Presentation

Acute Graft versus Host Disease (aGvHD) is a serious complication after allogeneic Hematopoietic Stem Cell Transplant (allo-SCT) and is a major cause of Transplant Related Mortality (TRM). Haploidentical allo-SCT (haplo-SCT) is increasingly utilized as it offers reliable and expeditious source for stem cells. However the incidence of aGvHD and high non-relapse mortality after haplo-SCT is a major concern. Glucocorticoids are still the gold standard therapy for aGvHD, but up to 50% of patients with acute gastro-intestinal and liver GvHD are steroid refractory and the outcome of such steroid refractory patients is universally poor. There are no standard of care guidelines for steroid-refractory aGVHD and various modalities have been tried. We report a patient with B-ALL who developed steroid-refractory grade IV aGvHD of gut and liver after haplo-SCT, which was successfully treated with alemtuzumab. To our knowledge, this is first case report of successful use of alemtuzumab for treatment of steroid refractory aGvHD in haplo-SCT.

A 36-year-old Hispanic male presented with one week history of cough and epistaxis. The total WBC was 102,000/microL at presentation and blood smear confirmed 90% blast cells. Bone marrow and flow cytometry studies confirmed the diagnosis of B-ALL. The cytogenetic studies revealed deletion of 9p21 and t (9;22) translocation, suggesting high risk nature of the disease. The patient received induction chemotherapy with multidrug regimen consisting of rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone. The interim bone marrow analysis showed presence of minimal residual disease with 3.2% of blast cells. The patient subsequently received salvage chemotherapy with phase 1 and 2 of MRC-ALL XII/ECOG E2993 protocol (details of chemotherapy protocol are already published). The patient achieved complete remission and haplo-identical SCT was performed in the first remission. He received CMV matched, T-cell replete haplo-SCT using Johns Hopkins non-myeloablative conditioning protocol. The patient received 6 x 10^6 CD34+ cells/kg peripheral blood stem cells from his son. The aGvHD prophylaxis included high-dose post-transplant cyclophosphamide, tacrolimus, and Mycophenolate Mofetil (MMF). The post-transplant recovery was complicated by elevated liver enzymes and bilirubin of 1.5 mg/dL on day 10. Subsequently patient developed severe nausea and diarrhea of 1700 ml/day on day 11 post-transplant. Subsequent colonoscopy and biopsy confirmed gut aGvHD and was diagnosed with

Grade IV GI GvHD and clinical Grade III GvHD of liver. The patient received treatment dose (2mg/kg/day) of methylprednisone for 8 days and supportive care, however diarrhea worsened and liver function deteriorated. The patient received alemtuzumab 60mg, in two divided doses 1 week apart. Within 24 hours of first dose of alemtuzumab, there was reduction in frequency and quantity of the stool volume from 2200 ml/day to 1400ml/day. After second dose of alemtuzumab, the diarrhea completely subsided and bilirubin continued to improve and normalized by day 62 post allo-SCT thus achieving complete remission.

He developed CMV viremia, on day 42 post allo-SCT with 32,123/mL CMV copies, and acute abdominal pain. CT abdomen revealed contained perforation around the appendix and he underwent laproscopic appendectomy and pathologic examination revealed CMV appendicitis [1]. This was treated with gancyclovir and CMV specific immunoglobulin infusions. His day 100 post haplo-SCT bone marrow examination was negative for any minimal residual disease by flow cytometry and the peripheral blood chimerism testing revealed 98% and >99% of CD3 and CD33 donor cells engraftment, respectively. He developed chronic GvHD of the mouth, eyes and skin (extensive) that started around day 150 post allo-SCT during taper of immune suppression and continues to remain on prednisone, MMF and tacrolimus with complete remission of chronic GVHD.

Steroid refractory aGvHD is defined as absence of response after 7 to 10 days of commencement of steroids or if the aGvHD clearly worsening 3 to 4 days after the steroids [2]. It is potentially life threatening condition with up to 95% mortality rate [3]. There is no standard of care for steroid refractory aGvHD patients and several agents such as Anti-Thymocyte Globulin (ATG), several monoclonal antibodies such as alemtuzumab, infliximab, rituximab, etanercept, photopheresis, sirolimus, pentostatin and mesenchymal "stem" cells have been tried, with a low durable complete response rates [1,2]. Alemtuzumab, a recombinant humanized monoclonal antibody targeting the CD52 antigen, has been used with variable success rate in treatment of steroid refractory aGvHD [4,5]. Two single institutional experiences reported alemtuzumab use in refractory gut aGvHD and resulted in an overall response rate of 64.2% and 70%, respectively [6,7]. A phase II study in 10 patients reported clinical response rate of 55% using alemtuzumab for steroid-refractory aGvHD in HLA identical allo-SCT recipients [8]. In this study, there were seven (70%) cases of CMV reactivation reported. A small prospective study for steroid refractory aGvHD in 15 patients reported an overall response rate of 67%, with 40% complete reponses [9]. The risk of non-relapse mortality in haplo-SCT is comparable to that of matched unrelated donor transplantation [10]. Our patient had grade III-IV steroid-refractory aGvHD with intestinal and liver involvement and had a complete response to alemtuzumab. The patient is currently D180 post haplo-SCT and is in complete remission from aGvHD although has extensive chronic GvHD of mouth, eyes and skin which is well controlled with re-institution of immune suppression and retains full donor chimerism. The use of alemtuzumab for steroid-refractory aGvHD in this setting was not previously described. To the best of our knowledge, this is the first case of steroid-refractory aGvHD following haplo- SCT that was successfully treated with alemtuzumab. The use of alemtuzumab should be considered for steroid refractory aGvHD in haplo-identical setting in younger patients with minimal Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) scores and this needs to be further investigated in a prospective study.

References

1. Deeg HJ. How I treat refractory acute GVHD. Blood. 2007;109(10):4119-26.
2. Holtan SG, Pasquini M, Weisdorf DJ. Acute graft-versus-host disease: a bench-to-bedside update. Blood. 2014;124(3):363-73.
3. Westin JR, Saliba RM, De Lima M, Alousi A, Hosing C, Qazilbash MH, et al. Steroid-refractory acute GVHD: predictors and outcomes. Adv Hematol. 2011;2011:601953.
4. Schub N, Gunther A, Schrauder A, Claviez A, Ehlert C, Gramatzki M, et al. Therapy of steroid-refractory acute GVHD with CD52 antibody alemtuzumab is effective. Bone Marrow Transplant. 2011;46(1):143-7.
5. Tey SK, Vuckovic S, Varelias A, Martins JP, Olver S, Samson L, et al. Pharmacokinetics and immunological outcomes of alemtuzumab-based treatment for steroid-refractory aGVHD. Bone Marrow Transplant. 2016;51(8):1153-5.
6. Meunier M, Bulabois CE, Thiebaut-Bertrand A, Itzykson R, Carre M, Carras S, et al. Alemtuzumab for severe steroid-refractory gastrointestinal acute graft-versus-host disease. Biol Blood Marrow Transplant. 2014;20(9):1451-4.
7. Schnitzler M, Hasskarl J, Egger M, Bertz H, Finke J. Successful treatment of severe acute intestinal graft-versus-host resistant to systemic and topical steroids with alemtuzumab. Biol Blood Marrow Transplant. 2009;15(8):910-8.
8. Martinez C, Solano C, Ferra C, Sampol A, Valcarcel D, Perez-Simon JA. Alemtuzumab as treatment of steroid-refractory acute graft-versus-host disease: results of a phase II study. Biol Blood Marrow Transplant. 2009;15(5):639-42.
9. Khandelwal P, Emoto C, Fukuda T, Vinks AA, Neumeier L, Dandoy CE, et al. A Prospective Study of Alemtuzumab as a Second-Line Agent for Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric and Young Adult Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2016;22(12):2220-5.
10. Mancusi A, Ruggeri L, Velardi A. Haploidentical hematopoietic transplantation for the cure of leukemia: from its biology to clinical translation. Blood. 2016;128(23):2616-23.