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Case Series

Pure Red Cell Aplasia - Post Major ABO Incompatible Allogenic Stem Cell Transplantation Role of Ibrutinib

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Abstract

Pure Red Cell Aplasia (PRCA) is a well-recognized complication of Major ABO-incompatible allogeneic stem cell transplantation. It is featured by anemia, Reticulocytopenia, and the absence of erythroblasts in a normal-appearing bone marrow biopsy. The mechanism for PRCA is presumed to be the persistence of recipient isoagglutinins, produced by residual host B lymphocytes or plasma cells, which probably interfere with the engraftment of donor erythroid cells. Several risk factors for PRCA have been reported, such as the presence of Anti-A Isoagglutininsbefore transplantation, reduced intensity conditioning, absence of Graft Versus Host Disease (GVHD), sibling donor and Cyclosporin A(CsA) as GVHD prophylaxis. PRCA is not a barrier to going ahead with Hematopoietic Stem Cell Transplantation (HSCT). There are many therapeutic options however few recover spontaneously, among the available options include high-dose steroids, Erythropoietin(EPO), Plasma exchange, Donor lymphocyte Infusion (DLI), treatment with Rituximab, Bortezomib, Daratumumab and tapering or discontinuation of immunosuppression. All these options have variable success in the literature ranging from 30% - 70%, Non-responders become red cell transfusion dependent and their quality of life is impaired. We are reporting a novel therapeutic option, Ibrutinib as an armamentarium in treating the PRCA post-HSCT, which works by blocking the Bruton Tyrosine Kinase (BTK) pathway thereby inhibiting the host B cell isoagglutinins production and good clinical response.

More Information

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Keywords: PRCA; Ibrutinib; ABO mismatch transplant; EPO; BTK inhibitor

Abbreviations: PRCA: Pure Red Cell Aplasia; CLL: Chronic Lymphocytic Leukemia; MCL: Mantle Cell Lymphoma; BTK: Bruton Tyrosine kinase; MAC: Myelo Ablative Conditioning; HCT: Hematopoietic Cell Transplantation; CSA: Cyclosporine; MTX: Methotrexate

Introduction

Pure red cell aplasia (PRCA), with a reported incidence of 10% - 20% [1], can occur following allogeneic stem cell transplantation if donor and recipient ABO blood groups are mismatched, with the recipient having isoagglutinins against the donor blood group [2]. Plasma cells that survive despite conditioning produce anti-ABO isoagglutinins which target donor erythroid precursors in the bone marrow thereby causing PRCA.PRCA occurred in about 7% of Major ABO mismatched HCTs it can present either as PRCA or pancytopenia [3].

Therapeutic options include steroids, discontinuation of immunosuppression, Bortezomib, rituximab, daratumumab, Elthrombopag, and donor lymphocyte infusion, all having a variable success [4]. Ibrutinib–small molecule tyrosine kinase inhibitor works against BTK receptor on B cells. We hypothesize that Ibrutinib would have an effect through the BTK pathway to attack the recipient residual B cells thereby reducing the production of isoagglutinins, which are the probable culprits for PRCS.

Here we are reporting three such cases successfully managed with Ibrutinib, patients became transfusion independent and their blood group changed in 4 weeks duration.

Case presentation

This is the retrospective study that collected data from the clinical registry, PRCA was confirmed by reticulocyte count followed by bone marrow aspiration and biopsy. Ethical committee approval was obtained and consent from the patient was also obtained.

Patient 1

A 17-year-old female was worked up for pancytopenia and diagnosed with severe aplastic anemia -46XX, PNH negative. She had a 10/10 HLA-matched male sibling, and undergone matched sibling donor (MSD) allogeneic stem

cell transplantation. She had Major ABO incompatibility with the donor (Recipient: O Rh^+ and Donor: B Rh^+). Received myeloablative conditioning chemotherapy with Fluderabine + Cyclophsophamide and Horse ATG, followed by peripheral blood stem cell infusion 7.5 x 10^6 CD_{34}, after RBC depletion. She received a short course of Methotrexate and cyclosporine as GVHD prophylaxis and had febrile neutropenia and grade 2 mucositis during the course. Engrafted for Neutrophil and platelets on Day+13 and D+15 respectively. She was discharged on day+20. On day+30 she had 99.4% full donor chimerism. However, she continued to have low hemoglobin and was on transfusion until Day+234, evaluated for the same and she was diagnosed to have PRCA. Tried Erythropoietin, tapering immunosuppression, and Bortezomib however no response. In view of financial constraints Rituximab and Daratumumab were not considered. She was initiated on Tab. Ibrutinib at 140 mg/day later escalated to 280mg/day and she had gradual improvement in hemoglobin and became transfusion independent, her anti-B titers were negative by Day+360, and her blood group was changed to donor blood group both forward and reverse grouping (Figure 1; Table 1). Ibrutinib was stopped 2 weeks after negative antibody titers. Currently, post-transplant 4yrs, doing well.

Patient 2

A 56-year-old gentleman diagnosed with Acute Myeloid Leukemia-High Risk received one cycle of induction chemotherapy (7 days of Cytarabine and 3 days of Daunorubicine) and one cycle of consolidation with high dose Cytarabine. He attained complete remission. In view of the high-risk disease and he had a fully HLA-matched sibling, allogeneic stem cell transplantation was considered. Received Myeloablative conditioning chemotherapy with Fluderabine and busulfan, he had major ABO incompatibility with the donor [Recipient: O Rh^+ and Donor: B Rh^+]. The stem cell dose was 7 x 10^6 CD_{34}/kg after RBC depletion, a short course of Methotrexate and cyclosporine as GVHD prophylaxis, had febrile neutropenia and grade 3 mucositis during the course. Engrafted for Neutrophil and platelets on Day+14 and D+17 respectively. He had CMV reactivation and hematuria managed conservatively. He continued to have low hemoglobin and was transfusion-dependent, and received 16 units of transfusion until Day+122 of the transplant. Diagnosed to have PRCA. Tried EPO, Rituximab, tapering of immunosuppression, and Bortezomib, however, he had no response therefore he was considered for Tab.Ibrutinib at 140 mg per day, within a week, showed improvement in hemoglobin and transfusion-independent, continued until antibody titers were negative (Figure 2; Table 2). Post-transplant currently 3 years, received vaccination and doing well.

Patient 3

A 13-year-old male child diagnosed to have HLH-PRF1 homozygous mutation, central nervous system involvement presented with Ataxic gait. After HLH 2004 protocol he attained remission on imaging. He underwent MSD [matched sibling Donor] allogeneic HSCT, with MAC conditioning regimen-Fluderabine, Treosulfan, and Thiotepa. He had bidirectional ABO incompatibility with the donor [Recipient: B Rh^+ and Donor: A Rh^+]. The stem cell dose was 5.8 x 10^6 CD_{34}/kg after RBC depletion, a short course of Methotrexate and cyclosporine as GVHD prophylaxis, and had febrile neutropenia and grade 3 mucositis during the course. Engrafted for Neutrophil and platelets on Day+12 and D+16 respectively, he was discharged on day+20. On day+30, had 100% full donor chimerism. By Day+73 he required a blood transfusion, evaluated, and diagnosed as PRCA with high Anti-B titers. In view of experience from the previous case, we considered Tab.Ibrutinib at 140 mg per day continued, however, he continued to receive blood transfusion and low retic count, later dose was escalated to 240 mg/m^2/day dose with changing dose he showed improvement in hemoglobin and retic count improved, transfusion independent.

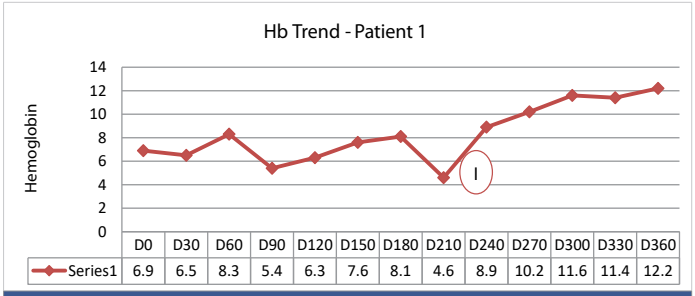

Figure 1: Patient 1 Hemoglobin trend.

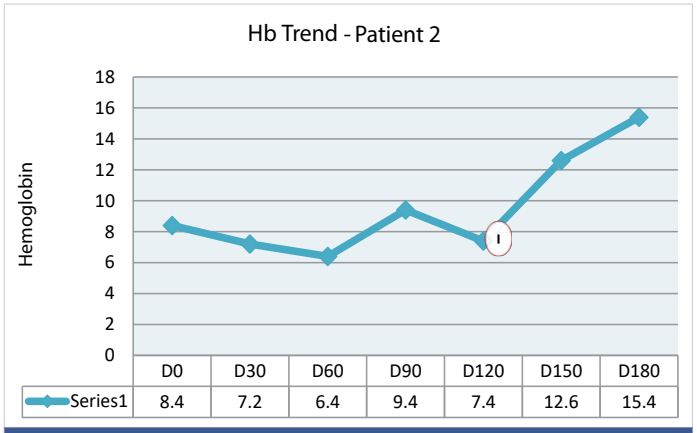

Figure 2: Patient 2 Hemoglobin trend.

Table 1: Patient 1 Anti A and B titers.

Patient 1	D+60	D+120	D+180	D+230	D+300	D+360
Anti A	1:32	1:32	1:32	1:32	1:32	1:128
Anti B	1:32	1:32	1:16	1:16	1:08	Negative

Table 2: Patient 2 Anti A and B titers.

Patient 2	D+30	D+60	D+90	D+120	D+150	D+180
Anti A	1:32	1:32	1:32	1:32	1:64	1:128
Anti B	1:32	1:32	1:16	1:32	1:16	Negative

Results

In this retrospective study, after ethical committee approval, data were collected from the care records and tabulated.

Patient-wise data was depicted in the table given below (Table 3).

Discussion

PRCA is a well-known effect of ABO mismatched allogeneic HCT, documented in about 7% of ABOi HCTs [5]. ABO mismatched transplants can produce either PRCA alone or PRCA with Pancytopenia [6]. Various agents have been used in the literature including pharmacological EPO agonists, Rituximab, Bortezomib, and Daratumumab, and Non-Pharmacological approaches like Tapering and stopping of immunosuppression, DLI, and stem cell boosting [7]. No standard of care for pure red cell aplasia (PRCA) after major ABO-incompatible hematopoietic stem cell transplantation (HSCT) has been established [8].

All these agents have variable success rates between 40% - 60%. Daratumumab, an anti-CD38 targeting antibody being tried in refractory cases of PRCA post HSCT [9]. In the literature, the majority of patients were blood group O, even in our series two patients were blood group O [3]. However, Ibrutinib though it is not yet approved for this indication there is one single center publication of 5 patient data [10]. Arslan S, et al. reported in their paper 5 case series presented as posters in ASTCT journal with a 100% success rate [7]. Our paper is the second in the literature for using Ibrutinib for PRCA post-HCT. The countries like India Ibrutinib is much more economical than other pharmacological agents in view of generic availability so it is also a cost-effective option [11]. Ibrutninb was well tolerated at a small dose of 140 mg per day, with no major adverse effects except for two patients who developed Periungual granuloma (Figure 3) which was treated with topical Boric acid [12]. Three patients became transfusion-independent within 4 weeks and the blood group was changed within 6 weeks, a similar pattern was demonstrated in the Arslan, et al. publication [7]. Our experience shows that Ibrutinib could give safe and effective therapeutic treatment option for Refractory PRCA post HCT. Prospective trails required to assess if early introduction would reduces the morbidity of transfusion, cost saving and GVHD complication if co-exist.

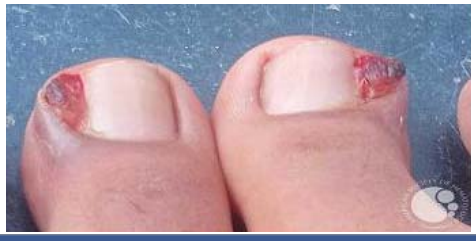

Figure 3: Periungual granuloma in patient 1.

Table 3: Patient data.

	Patient 1	Patient 2	Patient 3
Diagnosis	Severe Aplastic Anemia	AML-HR	HLH-PRF1+
Age/Sex	17 yrs/Female	56 yrs/Male	13 Yrs/Male
Recipient/Donor BG	O Rh^+/B Rh^+	O Rh^+/B Rh^+	B Rh^+/A Rh^+
HLA match	10/10	10/10	12/12
Conditioning regimen	MAC-Flu+CTx + ATGh	MAC-Flu+Bu	MAC-Flu+Treo+Thio
GVHD prophylaxis	MTX+CSA	MTX + CSA	MTX + CSA
N/P engraftment	D+13/D+15	D+14/D+17	D+12/D+16
Chimerism Day+30	99.4% Donor chimerism	100% donor chimerism	100% Donor Chimerism
Post HCT PRBC Transfusion >D+30	18 units of PRBC until D+234	16 units of PRBC until D+122	4 units of PRBC until D+73
BMA and Biopsy	Absent erythroid precursors Reticulocytopenia	Absent erythroid precursors Reticulocytopenia	Reticulocytopenia, PRCA
Pre Ibrutinib therapy	EPO, Bortezomib	EPO; Rituximab; Bortezomib	Blood Transfusion
Post Ibrutinib Transfusion	No further transfusions	No further transfusions	1 transfusion post Ibrutinib
Ibrutinib adverse effects	Periungal Granuloma	-	Periungal Granuloma

Conclusion

Pure Red cell aplasia post allogeneic stem cell transplant is one of the major morbidity, various modalities have been tried with heterogeneous success. Ibrutinib is a new armamentarium, which has shown near 100% response in the limited published data. It needs a large trial to confirm the findings.

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Authorship contributions

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References

1. Gao Y, Gao F, Shi J, Fu H, Huang H, Zhao Y. Successful treatment of refractory pure red cell aplasia with eltrombopag after ABO-incompatible allogeneic hematopoietic stem cell transplantation. J Zhejiang Univ Sci B. 2021;22(8):695-700. Available from: https://doi.org/10.1631/jzus.b2000532
2. Henig I, Yehudai-Ofir D, Zohar Y, Zuckerman T. Pure Red Cell Aplasia following ABO-Mismatched Allogeneic Hematopoietic Stem Cell Transplantation: Resolution with Daratumumab Treatment. Acta Haematol. 2021;144(6):683-687. Available from: https://doi.org/10.1159/000515257
3. Aung FM, Lichtiger B, Rondon G, Yin CC, Alousi A, Ahmed S, et al. Pure Red Cell Aplasia in Major ABO-Mismatched Allogeneic Hematopoietic Stem Cell Transplantation Is Associated with Severe Pancytopenia. Biol Blood Marrow Transplant. 2016;22(5):961-965. Available from: https://doi.org/10.1016/j.bbmt.2016.02.008

4. Bathini S, Holtzman NG, Koka R, Singh Z, Wilding E, Zou Y, et al. Refractory postallogeneic stem cell transplant pure red cell aplasia in remission after treatment with daratumumab. Am J Hematol. 2019;94(8):E216-E219. Available from: https://doi.org/10.1002/ajh.25515

5. Griffith LM, McCoy JP Jr, Bolan CD, Stroncek DF, Pickett AC, Linton GF, et al. Persistence of recipient plasma cells and anti-donor isohaemagglutinins in patients with delayed donor erythropoiesis after major ABO incompatible non-myeloablative haematopoietic cell transplantation. Br J Haematol. 2005;128(5):668-675. Available from: https://doi.org/10.1111/j.1365-2141.2005.05364.x

6. Seebach JD, Stussi G, Passweg JR, Loberiza FR Jr, Gajewski JL, Keating A, et al. GVHD Working Committee of Center for International Blood and Marrow Transplant Research. ABO blood group barrier in allogeneic bone marrow transplantation revisited. Biol Blood Marrow Transplant. 2005;11(12):1006-1013. Available from: https://doi.org/10.1016/j.bbmt.2005.07.015

7. Arslan S, Stein AS, Forman SJ, Nakamura R, Malki MMA. Ibrutinib for Pure Red Cell Aplasia after Allogeneic Hematopoietic Stem Cell Transplant with Major ABO Incompatibility. Biol Blood Marrow Transplant. 2020 Mar 1;26(3):S362-S363. Available from: https://doi.org/10.1016/j.bbmt.2019.12.195

8. Hirokawa M, Fukuda T, Ohashi K, Hidaka M, Ichinohe T, Iwato K, et al. PRCA Collaborative Study Group. Efficacy and long-term outcome of treatment for pure red cell aplasia after allogeneic stem cell transplantation from major ABO-incompatible donors. Biol Blood Marrow Transplant. 2013;19(7):1026-32. Available from: https://doi.org/10.1016/j.bbmt.2013.04.004

9. Chapuy CI, Kaufman RM, Alyea EP, Connors JM. Daratumumab for Delayed Red-Cell Engraftment after Allogeneic Transplantation. N Engl J Med. 2018;379(19):1846-1850. Erratum in: N Engl J Med. 2019;380(3):302. Available from: https://doi.org/10.1056/nejmoa1807438

10. Arslan S, Ali H, Mei M, Marcucci G, Forman S, Nakamura R, et al. Successful treatment of refractory pure red cell aplasia in major ABO-mismatched allogeneic hematopoietic stem cell transplant with single agent Ibrutinib. Bone Marrow Transplant. 2022;57(5):830-833. Available from: https://doi.org/10.1038/s41409-022-01590-0

11. Sathyanarayanan V, Flowers CR, Iyer SP. Comparison of Access to Novel Drugs for Lymphoma and Chronic Lymphocytic Leukemia Between India and the United States. JCO Glob Oncol. 2020;6:GO.20.00012. Available from: https://doi.org/10.1200/GO.20.00012

12. Ranjit Kumar Kumar CS, MD; Harshitha Aribandi. PRCA post allogenic transplant-Ibrutinib induced periungal granuloma 1. 2022. Available from: https://imagebank.hematology.org/imageset/60368/ibrunib-induced-periungal-granuloma