Abstract:
Conventional platelet transfusion may not be adequate to deal with platelet transfusion refractoriness (PTR), and therefore human leukocyte antigen (HLA) or human platelet antigen (HPA) matched and platelet crossmatch compatible units are recommended. However, in developing countries, finding a unit that is HLA or HPA matched or platelet crossmatch poses a challenge. Hence, easier and cost-effective alternatives such as massive platelet transfusion and continuous platelet transfusion were attempted to manage bleeding in PTR. A 31-year-old male presented with acute myeloid leukemia relapse and chloroma in bladder underwent FLAG salvage chemotherapy. Despite almost daily platelet transfusion with single donor platelets (SDPs), patient presented with hematuria and low corrected count increment at 1 h and 24 h suggesting both immune and nonimmune refractoriness to platelet transfusion. The patient received SDP transfusion twice daily from day 19 to day 21 to maintain hemostasis. The patient had persistent hematuria, so massive platelet transfusion in the form of double adult doses of SDP given every 12th hourly for three events. Despite these measures, there was persistent hematuria and refractoriness to platelet transfusion. As HLA or HPA matched or crossmatch compatible platelets were unavailable, continuous platelet transfusion was started for this patient from day 23 to day 28. After 4 days of continuous platelet transfusion, hematuria subsided. In resource-constrained clinical settings, continuous platelet transfusion can be an effective alternative to HLA/HPA-matched platelets in the management of PTR.

Keywords:
Continuous platelet transfusion, corrected count increment, massive platelet transfusion, platelet transfusion refractoriness

Introduction
Platelet transfusion support is a critical part in the treatment of acute myeloid leukemia (AML). Platelet transfusion refractoriness (PTR) describes a clinical state, in which the anticipated rise in platelet count from a platelet transfusion is not achieved. PTR is a serious and common complication observed in 15%–25% of patients receiving treatment for leukemia [1,2]. Therapeutic effectiveness of platelet transfusion is objectively measured with the corrected count increment (CCI). Transfusion of human leukocyte antigen (HLA) or human platelet antigen (HPA) compatible platelets is the cornerstone for patients who are refractory...
to platelet transfusions because of the development of alloantibodies against Class I HLA or HPA expressed on platelets.[2]

PTR has been linked to inferior clinical outcomes including bleeding and mortality, as well as higher health-care costs.[2] The efficacy of HLA-matched transfusion in PTR setting was observed to be only 40%–50%.[3]

In developing countries, finding an HLA or HPA-matched unit or platelet crossmatch compatible unit poses a huge challenge. When patients with PTR have no HLA/HPA-compatible platelet donors or in the setting of ongoing bleeding, massive platelet transfusion, and continuous platelet transfusion commonly known as “platelet drips” were attempted with varied results.[2,3,6]

There are few reports in the literature about continuous platelet transfusion as an alternative method for managing bleeding in PTR.[2,3,6] Here, we discuss one such case of AML with extramedullary involvement presenting with active bleeding with PTR managed using continuous platelet transfusion.

**Case Report**

A 31-year-old male diagnosed as AML in complete remission for 1 year presented with febrile illness, hematuria (WHO Grade 2 bleeding), and acute retention of urine. Ultrasound (USG) abdomen performed outside showed a bladder mass with impression, possible bladder chloroma, suggestive of AML relapse. The patient was treated for febrile neutropenia on day 1 of admission with empirical antibiotics, five units of platelet concentrates (PC), and two units of packed red cells was transfused for low hemoglobin and platelet count.

On day 6 of admission, cystoscopy done under platelet transfusion cover showed bosselated mass occupying posterior bladder wall with no evidence of active bleeding spots. Tissue biopsy from the mass confirmed the presence of extramedullary involvement as bladder chloroma. Continuous irrigation of bladder was recommended for hematuria bone marrow aspirate and trephine biopsy showed hypercellular bone marrow with 57% myeloblasts and 31% monocyte lineage which was consistent with AML relapse. From day 11 to 15, FLAG chemotherapy regimen was administrated for AML relapse. The patient received almost daily single donor platelet (SDP) transfusion from days 7 through day 18 in view of ongoing hematuria and low platelet count [Figure 1]. Despite daily platelet transfusion, patient presented with persistent hematuria and low CCI suggesting refractoriness to platelet transfusion.

In view of PTR and to maintain hemostasis, increased dose of platelet transfusion was attempted by transfusing SDP units twice daily from day 19 to day 21. However, patient had persistent hematuria and hence 8 gray single fractions, palliative hemostatic radiation therapy was performed to bladder on day 23 with massive platelet transfusion (i.e., two adult doses of SDP) given every 12th hourly. Massive platelet transfusion was continued for three events with poor CCI. As HLA or HPA matched or crossmatch compatible platelets were unavailable, continuous platelet transfusion was started for this patient. The double dose SDP (yield of 6 × 10^11) was divided into six aliquots, each aliquot containing 1 × 10^11 platelets was transfused over 4 h from day 23 to day 28. After 4 days of continuous platelet transfusion, hematuria subsided. Pronounced fall of blood counts was noticed from day 18 to day 28 and counts started improving from day 29 to discharge [Figure 1]. Continuous platelet transfusions helped in maintain the endothelial integrity as evidenced by no new bleeding events.

On day 26 of initiation of chemotherapy, repeat USG abdomen was performed for response assessment and found that the tumor size had decreased. After 6 days of continuous platelet infusion, the platelet counts elevated, and no further bleeding was observed during the hospital stay [Table 1 and Figure 1]. During entire admission, the patient received 6 units packed red blood cell, 8 Units fresh frozen plasma, 20 units of PC, and 29 SDP units.

**Discussion**

Hemato-oncological conditions often present with disease or therapy-related hypoproliferative thrombocytopenia. These patients require regular prophylactic platelet transfusions to reduce the risk of bleeding. Although the pathology behind the immune and nonimmune causes differ, they frequently coexist in certain patients such as those with AML.[1] The present patient had fever, bleeding, and sepsis, chemotherapeutic drugs with poor CCI at 1 and 24 h, describing the possibility of both immune and nonimmune mediated PTR.
Methods commonly employed to assess the efficacy of platelet transfusions include, platelet count increment, frequency, and severity of bleeding. Interval between transfusion and number of units of red blood cell transfused was also used as surrogate marker for assessing the efficacy of platelet transfusion. Hemostatic assays have shown promising results in determining the needs of transfusion in trauma and surgical hemorrhage; however, such assays are yet to be validated in predicting clinically significant bleeding in thrombocytopenic patients. Patients with AML and extramedullary involvement are more susceptible for PTR. The common sites of extramedullary involvement are lymph nodes, liver, and spleen. Comont et al. observed increased risk for PTR when AML presenting with extramedullary involvement (odds ratio = 4.87 [1.75–13.54], P = 0.002). The present patient also had AML with extramedullary involvement in the unusual site such as urinary bladder, where the probability of bleeding is very high.

Recent guidelines recommend the use of HLA or HPA‑matched platelets or crossmatch compatible platelets in PTR patients. However, highly alloimmunized patients with refractory bleeding can be very difficult to manage, especially when they do not respond to any platelets including crossmatch compatible, antigen negative, and HLA‑matched platelets. In these cases, limited success has been achieved with massive or continuous transfusion of ABO identical platelets, use of high‑dose intravenous immunoglobulin, splenectomy, and plasma exchange. Epsilon aminocaproic acid and Tranexamic acid may also be useful in reducing bleeding in these patients. In present case report, massive platelet transfusion and continuous platelet transfusion helped in successfully managing a bleeding AML patient with PTR.

**Literature review for the preparation of platelet units for continuous platelet transfusion**

An adult patient with a total blood volume ranging from 5 to 7 L will require a total of 0.36 × 10^{11} to 0.50 × 10^{11} platelets per day for maintaining hemostasis. Various methods to make split units for continuous platelet transfusion have been enumerated in literature. Cid et al. had split PCs containing 0.5 × 10^{11} into two units so that each half was infused over 4 h to comply with the standard of expiration of an open system. In Tzadok et al. and extended small dose platelet transfusion group, patients received a continuous 24 h SDP transfusion with each dose comprising 1.5 × 10^{11} platelets given over 4 to 6 h. In the present patient, double dose SDP was divided into six aliquots with 1 × 10^{11} platelets in each aliquot transfused over 4 h in closed system.

The duration of thrombocytopenia and hematuria was 32 days and 13 days, respectively. Table 1 summarizes platelet count at morning before 24 h platelet infusion, duration of 24 h infusion of platelets, and median platelet count at morning during 24 h platelet infusion.

Hematuria was controlled after 4 days of continuous platelet transfusion and no adverse event was noticed in this patient [Figure 2]. Similarly, in Cid et al. study, hemorrhage was disappeared in all cases during the 24 h continuous infusion and reported no transfusion reactions with continuous transfusion.

Mazzara et al. reported an increase of deposition of fibrin on the subendothelial surface after transfusing HLA‑incompatible platelets as continuous platelet

| Characteristics of the patient | Present case report |
|-------------------------------|---------------------|
| Duration of thrombocytopenia (days) | 32 |
| Platelet count at morning before 24 h platelet infusion (×10^{9}/L) | 6 |
| Duration of 24 h infusion of platelets (days) | 6 |
| Median platelet count at morning during 24 h platelet infusion (×10^{9}/L) | 2 (1-10) |
| Duration of WHO Grade 2 bleeding (days) | 13 |
| Median preplatelet count during hospital stay (×10^{9}/L) | 14 (4-18) |
| Median postplatelet count during hospital stay (×10^{9}/L) | 13 (2.5-17) |
| Median white blood cell count during hospital stay (×10^{9}/L) | 2.4 (0.3-9.35) |
| Median hemoglobin during hospital stay (g/dL) | 7.8 (7.15-9.35) |
| Median platelet dose transfused during hospital stay (×10^{11}) | 3.15 (2.56-6.0) |

Figure 2: Corrected count increment at 24 h and preplatelet count of the patient during platelet transfusions
transfusion, measured using ex vivo experiments with Baumgarten’s platelet adhesion model.[12] Continuous platelet transfusion using double dose platelets also had the added advantages of reducing the number of donor exposure and reducing the cost associated with massive transfusion. Hence, continuous platelet transfusion can be an effective approach to the treatment of platelet refractoriness in patients treated for hematological malignancies in resource-poor setting.

**Conclusion**

Continuous platelet transfusion is a feasible and safe alternative to HLA/HPA-matched platelets in the management of PTR in patients with hematological malignancies in resource-constrained clinical settings.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Comont T, Tavitian S, Bardiaux L, Fort M, Debiol B, Morère D, *et al.* Platelet transfusion refractoriness in patients with acute myeloid leukemia treated by intensive chemotherapy. Leuk Res 2017;61:62-7.

2. Cid J, Guijarro F, Carbassé G, Lozano M. 24-h continuous infusion of platelets for patients with platelet transfusion refractoriness. Br J Haematol 2018;181:386-9.

3. Gurevich-Shapiro A, Tzadok S, Rosenberg A, Inbal A, Bar-Natan M, Wolach O, *et al.* Extended small-dose platelet transfusions in multitransfused hemato-oncological Patients: A single-center experience. Acta Haematol 2017;137:183-90.

4. Hod E, Schwartz J. Platelet transfusion refractoriness. Br J Haematol 2008;142:348-60.

5. Fasano RM, Josephson CD. Platelet transfusion goals in oncology patients. Hematology Am Soc Hematol Educ Program 2015/2015:462-70.

6. Tzadok S, Gurevich A, Inbal A, Bar-Natan M, Wolach O, Raanani P. Continuous platelet transfusion increases platelet increment in refractory hemato-oncological patients – A single center experience. Blood 2014;124:2888.

7. Ganzel C, Manola J, Douer D, Rowe JM, Fernandez HF, Piaietta EM, *et al.* Extramedullary disease in adult acute myeloid leukemia is common but lacks independent significance: Analysis of patients in ECOG-ACRIN cancer research group trials, 1980-2008. J Clin Oncol 2016;34:3544-53.

8. Stanworth SJ, Navarrete C, Estcourt L, Marsh J. Platelet refractoriness--practical approaches and ongoing dilemmas in patient management. Br J Haematol 2015;171:297-305.

9. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, *et al.* Clinical guideline platelet transfusion: A clinical practice guideline from the AABB. Ann Intern Med 2015;162:205-13.

10. Schiffer CA, Bohlke K, Delaney M, Hume H, Magdalinski AJ, McCullough JJ, *et al.* Platelet transfusion for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2018;36:283-99.

11. Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, *et al.* Guidelines for the use of platelet transfusions. Br J Haematol 2017;176:365-94.

12. Mazzara R, Escolar G, Garrido M, Sanz C, Pereira A, Castillo R, *et al.* Procoagulant effect of incompatible platelet transfusions in alloimmunized refractory patients. Vox Sang 1996;71:84-9.