Case Report

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Therapeutic leukapheresis in a tertiary care hospital: A case series

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Abstract:

Patients presenting with hyperleukocytosis secondary to acute leukemia, with total leukocyte count or blast count more than 100,000/μL are often considered for leukapheresis, especially if clinical signs of leukostasis are present. Leukostasis is often associated with high morbidity and mortality in patients with leukemic processes. The main goal of management of hyperleukocytosis and/or leukostasis is to reduce the blast count before initiation of chemotherapy. Leukapheresis is often used prophylactically to prevent leukostasis or to provide symptomatic relief. We, as transfusion medicine specialists, present our experience of doing therapeutic leukapheresis in patients presenting with hyperleukocytosis with or without presenting features of leukostasis.

Key words:

Hyperleukocytosis, leukapheresis, leukoreduction, leukostasis, total leukocyte count

Hyperleukocytosis is a condition characterized by an increase in total leukocyte count (TLC) or blast count to more than 100,000/mm^3.[1-3] It is usually seen in 5–18% of adults diagnosed with acute myeloid leukemia (AML) depending on the leukemic subtype.[3] Early complications resulting in high morbidity and mortality is seen in these patients due to leukostasis, a microcirculatory dysfunction caused by the sludging of the leukemic blast cells in capillary vessels and their resultant deleterious effects.[2-4] Majority of deaths are due to intraparenchymal brain hemorrhage and/or respiratory failure.[2]

Leukoreduction is achieved either by leukapheresis or chemotherapy.[3] Therapeutic leukapheresis is usually initiated as soon as clinical signs of leukostasis appear[2] and is preferred due to the immediate cytoreductive effect, resulting in rapid improvement in the patient's condition.[4] Although a widely used approach, many clinicians still prefer the conservative approach of using chemotherapy as it is less invasive.[5] In this case series, we present our experience as transfusion medicine specialists in treating patients of hyperleukocytosis leukemia with therapeutic leukapheresis.

Methods

This study was conducted in the Department of Transfusion Medicine, Indraprastha Apollo Hospital, New Delhi, from July 2014 to December 2015. Therapeutic leukapheresis was performed with Haemonetics MCS+ cell separator (Braintree, MA, USA) using central venous access. ACD-A was used as anticoagulant with ACD-A:blood ratio of 1:12. Whole blood inlet flow rate and collection flow rate were adjusted by the system according to the size of the patient (sex, height, and weight) to reduce the risk of procedure-related complications such as citrate toxicity. The complete blood count pre- and post-procedure was performed on Beckman Coulter LH750. All procedures were done after due consent of the patient.

Case Reports

Case 1

A 25-year-old male complained of sore throat and fever with chills and rigors for 1 month, petechial hemorrhages for 20 days, and unexplained weight loss. He revealed a history of cigarette smoking (2–3/day). On examination, the patient had subconjunctival hemorrhage, petechiae,

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hepatosplenomegaly, and bilateral submandibular and cervical lymphadenopathy. His baseline investigations at the time of admission showed hemoglobin (Hb) – 7.5 g/dl, TLC – 301,000/μL, and platelet count (PLT) – 20,000/μL. The patient was diagnosed as a case of biphenotypic acute leukemia (myeloid/T-cell) based on flow cytometry and bone marrow biopsy (97% blasts). The patient was immediately started on intravenous hydration, antibiotics, and steroids for hyperleukocytosis.

On day 4, the patient developed altered sensorium and shortness of breath with further deterioration needing ventilator support. An increase in TLC (321,200/μL) was also noted. Emergency therapeutic leukapheresis was initiated. One blood volume (3.5 L) was processed, and 359 ml of ACD-A was used. The reduction in TLC was 156,200/μL (49%) [Table 1]. No adverse events or procedure-related complications were reported. Postleukapheresis, the patient, was transfused with 1 unit of packed red blood cells (PRC) and 1 unit of PLT on cell separator (POCS) (23% reduction in PLT count) and was started on vincristine and daunomycin, followed by addition of L-Asparaginase (day + 2 postleukapheresis). The patient improved symptomatically and was gradually weaned of assisted ventilatory support. The patient was discharged on day 29 in hemodynamically stable condition. On follow-up (6 months), patient is asymptomatic and doing well.

Case 2

A 28-year-old male, known case of chronic myeloid leukemia (CML) on dasatinib, complained of headache and vomiting for 2 days and was found to have high TLC (102,100/μL) on routine follow-up. Bone marrow biopsy revealed relapsed disease with blast crisis (96% blasts) for which two leukapheresis procedures were performed on consecutive days.

During the first procedure, one blood volume (2.5 L) was processed, whereas in the second, two blood volume (5 L) was processed, and a total of 542 ml of ACD-A was used. The reduction in TLC was 5200/μL (5%) after the first procedure and 18,100/μL (19%) after the second procedure [Table 1]. Patient experienced mild symptoms of citrate toxicity during the first procedure, which was managed effectively with calcium infusion and fall in PLT count by 28,000/μL from baseline levels (41% reduction) was noted after the first procedure for, which patient was transfused with 1 unit of POCS. After the second procedure, patient was started on hydroxyurea and antitumor lysis therapy and was transfused with 1 unit of POCS. No induction chemotherapy given. The patient was discharged (day 18) on dasatinib and advised for further follow-up on an outpatient basis. On follow-up (3 months), the patient was asymptomatic and doing well. Subsequently, the patient was lost to follow-up.

Case 3

A 69-year-old male, known diabetic, hypertensive, chronic kidney disease with anemia of chronic disorder, was admitted to our center with a history of irrelevant talks, distension of abdomen, and with high TLC (87,100/μL). On examination, hepatosplenomegaly was found. The patient was diagnosed as a case of myelodysplastic syndrome with myelofibrosis (Janus kinase-2 positive). On day 2, the patient developed difficulty in breathing for which oxygen support was given. Leukapheresis was planned to provide symptomatic relief. One blood volume (3 L) was processed, and 281 ml of ACD-A was used. The reduction in TLC was 32,900/μL (38%) [Table 1]. A fall in PLT count by 17% from the baseline was noted; however, the patient was not transfused. There were no procedure-related complications. No induction chemotherapy given. The patient was discharged on day 4, on hydroxyurea and prednisolone with advice to follow-up on outpatient basis. One month

Table 1: Patient characteristics and details of therapeutic leukapheresis procedures

	Patient 1	Patient 2	Patient 3	Patient 4
Age/sex	25/male	28/male	69/male	27/male
Diagnosis	Biphenotypic acute leukemia	Chronic myeloid leukemia	Myelofibrosis (JAK-2 positive)	Acute myeloid leukemia - M4
Preprocedure				
Hb (g/dL)	6.4	11.6	10.3	6
TLC (/μL)	321,200	102,000	87,100	112,000
PLT (/μL)	51,000	68,000	29,000	12,000
Postprocedure				
Hb (g/dL)	6	9.5	8.9	6.7
TLC (/μL)	165,000	78,800	54,200	17,800
PLT (/μL)	39,000	67,000	24,000	29,000
Percentage reduction in TLC	49	5, 19	38	84
Transfusion				
Preprocedure	No	No	No	Yes (RDP)
Postprocedure	Yes (PRC, POCS)	Yes (POCS, after the first and second procedure)	No	Yes (PRC, RDP)
Hydroxyurea	Not given	Given (postleukapheresis)	Given (postleukapheresis)	Not given
Induction chemotherapy	Vincristine, daunomycin, L-asparaginase	No	No	Cytarabine and daunomycin
Procedure-related complications	No	Yes (relieved with calcium supplementation)	No	No
Follow-up status	Alive (6 months)	Alive (3 months)	Died (40 days after leukapheresis)	Died (30 days after leukapheresis)

Hb = Hemoglobin, TLC = Total leukocyte count, PLT = Platelet, RDP = Random donor platelets, POCS = Platelet on cell separator, PRC = Packed red blood cells, JAK-2 = Janus kinase-2

postprocedure, patient was readmitted with history of passage of blood mixed with stool, fever, and weakness for 2 days and later, the patient succumbed due to internal bleeding and septic complications (day 40 after leukapheresis).

Case 4

A 27-year-old male complained of weakness and headache for 2 months, conjunctival bleed, gum bleeding, epistaxis, and hematuria for 2 days. On examination, the patient had bilateral swelling of the eyes with severe ecchymotic patches all over the body. His baseline investigations at the time of admission showed Hb – 6 g/dL, TLC – 112,000/μL (neutrophils – 14%, lymphocytes – 8%, monocytes – 5%, and blasts – 52%), PLT – 12,000/μL, lactate dehydrogenase – 1530 U/L. The patient was diagnosed as a case of AML – M4 on the basis of flow cytometry and bone marrow biopsy. The patient was transfused with 6 units of random donor platelets (RDPs) in view of low PLT counts. Therapeutic leukapheresis was planned as a prophylactic procedure (day 0). One and half blood volume (5.3 L) was processed, and a total of 594 ml of ACD-A was used. The reduction in TLC was 94,200/μL (84%) [Table 1]. The procedure was uneventful. The patient was transfused with 1 unit of PRC and 4 units of RDPs postleukapheresis. With gradual improvement in the general condition of patient and chemotherapy was started on day 6 (cytarabine and daunomycin). Following the first session of chemotherapy, patient developed persistent fever with hematuria. Blood culture revealed Gram-negative bacilli and antibiotics were started as per sensitivity. On day 30, the patient succumbed due to septic complications.

Discussion

Hyperleukocytosis is associated with complications such as leukostasis, tumor lysis syndrome, and disseminated intravascular coagulopathy (DIC), which are associated with high risk of early deaths in these patients.[6,7] The symptoms suggestive of leukostasis are confusion, dizziness, headache, tinnitus, visual disturbances such as blurred vision, mental status change like stupor, delirium, coma or respiratory symptoms such as dyspnea, tachypnea, and hypoxemia.[7]

According to Ganzel *et al*.,[7] leukapheresis needs to be initiated when there is a compromise in the functioning of either one of the respiratory, central nervous system, or renal systems or when the leukocyte or blast count is more than 100,000/μL. The clinical efficacy of the procedure is best monitored with pre- and post-procedure TLC along with the patient's clinical condition. They reported that a single procedure results in 20–50% reduction in leukocyte or blast count.[7]

Critical leukocyte count resulting in leukostasis can be different, as in a case of AML, leukocyte count of 50,000/μL can result in severe symptoms whereas in CML, counts as high as 500,000/μL can be asymptomatic. The reason being that the patients of chronic leukemia tolerate hyperleukocytosis better than acute leukemia's because the cells are mostly differentiated and tend to sequester in the liver and spleen.[2]

The initial treatment given to these patients is usually supportive care, and the clinician needs to decide whether cytoreduction in the form of chemotherapy and/or hydroxyurea and/or leukapheresis is required or not.[4-6] As per the guidelines published by the American Society for Apheresis (ASFA), therapeutic leukapheresis is category I (Grade 1B) indication for symptomatic leukapheresis and category III (Grade 2C) for prophylactic procedures.[6] Ranganathan *et al*., discussed that Freirich *et al*., were the first ones to describe hyperleukocytosis and they have reported that patients with TLC count more than 200,000/μL show clinical evidence of leukostasis.[1] For patients presenting with symptomatic hyerpleukocytosis with leukostasis, emergency therapeutic leukapheresis is done. For patients with symptomatic hyperleukocytosis only, induction chemotherapy (cytarabine and daunomycin) is started, provided there are no contraindications for immediate intensive induction treatment such as severe metabolic disturbances or renal insufficiency. In such cases, hydroxyurea can be used for cytoreduction.[8] For patients presenting with asymptomatic hyperleukocytosis, patients are assessed for the risk of TLS, DIC or development of leukostasis, in case there is a risk, leukapheresis is attempted. Leukostasis can even occur when the blast count is 50,000–100,000/μL probably due to the unique features of some leukemic blasts such as activation of cell surface markers for adhesion to endothelium and cell to cell interaction, therefore, leukapheresis can be done as a temporizing measure until chemotherapy can be initiated. Given, the safety of the leukapheresis procedure clinicians are not reluctant in withholding leukapheresis for patients presenting with only hyperleukocytosis, despite no published randomized trial for such patients.[9] The decision to perform leukapheresis was very much based on the discretion of the attending clinician, and the main deciding factors for performing leukapheresis were clinical status of the patient and/or TLC more than 100,000/μL in our hospital.

Two of our patients (case 1 and 4) had TLC counts more than 100,000/μL, of which one was symptomatic, suggestive of leukostasis. In the other patient, the procedure was done prophylactically, to reduce the risk of tumor lysis syndrome,[1] as he had high blast counts (52%). Both the patients had predominantly myeloid cells and rapid reduction in TLC was seen to 49% and 84% respectively after leukapheresis. However, in another patient (case 2) who also had TLC more than 100,000/μL, the clinical signs suggestive of leukostasis were not seen. The procedure was planned prophylactically due to high blast count on repeat biopsy (96%). More reduction in TLC was seen in second procedure compared to first which could be due to mobilization of sequestered blast cells adhered to endothelium and from the organs (bone marrow, spleen, and liver).

Leukapheresis was done in case 3 as a temporary measure to provide symptomatic relief, and subsequently, counts were controlled with hydroxyurea and prednisolone. Mangan and Luger[10] have also reported a similar case, where patient was initially diagnosed as a case of low-risk myelodysplastic syndrome before transformation to AML and leukapheresis was attempted in this patient to provide symptomatic relief due to signs suggestive of leukostasis and high TLC. However, our patient developed internal bleeding and septic complications and later succumbed 40 days post leukapheresis.

As per the ASFA recommendations, at least 1.5–2 blood volumes should be processed to achieve sufficient leukoreduction.[11]

However, for 3 of our patients (case 1–3) only one blood volume were processed. Tan *et al*.,[2] did a retrospective study in 14 patients presenting with hyperleukocytic leukemia in their institution and processed one blood volume for their patients and observed that a single efficient cycle of leukapheresis can result in decrease in leukocyte count by 31.9%. Similar study done by Parra Salinas *et al*.,[12] over a period of 9 years in 13 patients state that after an average of two sessions, a statistically significant reduction in TLC counts was seen. The results seen in our cases are in terms with the reported studies. Only one patient in our case study underwent two sessions of leukapheresis resulting in only 24% reduction in TLC. The probable reason being that patient was a case of CML and most of the leukemic cells were sequestered. More aggressive leukapheresis helps in achieving better reduction in blast count. However, there is always a possibility that even after significant removal of leukocyte or blast cells the circulating number of these cells may remain unmodified due to rapid mobilization of cells sequestered in spleen, liver, and bone marrow.[3]

Patients can present with varying degrees of red cell or PLT loss during leukapheresis procedure, especially when multiple procedures are performed.[7] Röllig and Ehninger recommend prophylactic PLT transfusions to maintain a count of 20,000–30,000/μL or 50,000/μL in case of full heparin anticoagulation until there is reduction in leukocyte count, and the clinical condition of the patient has stabilized.[8] Similar protocol was followed for our patients. We observed that only one of our patients (case 4) was transfused with PLTs before the leukapheresis, in view of low PLT counts. After the leukapheresis, three patients (case 1, 2, and 4) were transfused prophylactically to avoid any complication related to thrombocytopenia due to procedure itself or underlying etiology of the disease. We cannot comment about the percentage reduction in PLTs for case 4 as he was transfused both pre- and post-leukapheresis, and the counts were checked after the transfusion postleukapheresis. For case 2, patient was transfused after the first procedure due to 41% reduction in PLT count from baseline (68,000/μL), followed by which another procedure was done, and patient was transfused again after procedure and the counts were checked after the transfusion post second procedure; therefore, we cannot comment about percentage reduction after the second procedure.

In our set of patients, therapeutic leukapheresis was found to be effective in terms of rapid leukoreduction as chemotherapy might take 24–48 h to achieve the same effect of leukoreduction.[1] It was the combined effect of induction chemotherapy and/or hydroxyurea and leukapheresis which was found to be beneficial in our patients. However, larger studies are required to determine whether leukapheresis has any effect on the outcomes of such patients in terms of mortality.

Conclusion

Leukostasis secondary to hyperleukocytosis is a life-threatening complication of acute leukemia carrying poor prognosis due to high risk of morbidity and mortality. Therefore, leukapheresis, if available, can be performed without delaying the supportive treatment with hydration and chemotherapy, as it is relatively safe and effective treatment modality resulting in significant reduction in leukocyte or blast count.

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Conflicts of interest
There are no conflicts of interest.

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