

Research Article

Observational Study of Transfusion Support and Hemorrhagic Tendencies in Newly Diagnosed Patients of AML Undergoing Chemotherapy

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Abstract

Background: Transfusion support is an important and integral aspect for management of Acute Myeloid Leukemia (AML) as substantial amount of blood components may be required per patient during course of chemotherapy. We undertook this study to evaluate the quantitative aspect of blood component support in newly diagnosed AML patients undergoing chemotherapy. We also documented bleeding outcomes during the course of treatment.

Methods: Newly diagnosed 19 patients who opted for chemotherapy were included in the study. Quantitative transfusion details throughout the chemotherapy were recorded. Presence of fever, bleeding, infection/sepsis and splenomegaly, use of medications such as chemotherapeutic agents, AMB, G-CSF and antifibrinolytics were noted before every transfusion.

Results: Mean requirement of Leucopoor Red Blood Cells (LPRBC), Random Donor Platelets (RDP) and Fresh Frozen Plasma (FFP) was 14, 81.6 and 10 units respectively. Transfusion needs were more during induction as compared to consolidation phase of chemotherapy. Bleeding was noted on 19.7 % patient days. Modified WHO grade 1 bleeding was observed on 115 days (8.8%) followed by grade 2 (6.6%) and grade 3 (4.2%). Gastrointestinal tract bleeding was seen on 28.5% bleeding days followed by bleeding from oropharynx which was present on 19.1% bleeding days. No bleeding related mortality was noted.

Conclusion: The study provided insights into the complex issues of transfusion requirement of AML patients. We emphasize individualizing transfusion management of these patients as clinical factors are the major determinants of transfusion requirements. We also recommend that bleeding grades should be used as an outcome measure when determining the efficacy of platelet transfusions.

Keywords: Acute myeloid leukemia; Transfusion; Red blood cells; Platelets; Chemotherapy; Bleeding

Introduction

Over the past three decades, chemotherapy regimens and supportive care have been extensively improved and major advances have been made in the diagnosis and management of acute myeloid leukaemia (AML) [1]. Patients with acute leukemia usually present with features of bone marrow failure and symptoms and signs related to anemia, thrombocytopenia and infections. Hemostatic abnormalities are common occurrences in these patients in as much as 50% of patients have platelet counts $<50 \times 10^3/\mu\text{l}$ [2]. Clinically thrombocytopenia in these patients manifests as easy bruising, petechiae, epistaxis, gingival bleeding, conjunctival hemorrhages, and prolonged bleeding from skin injuries. Recent studies have elucidated coexistent thrombocytopathies in form of defective platelet aggregation, inadequate 5-hydroxytryptamine release and poor granulations [3]. In addition occasional patients may also experience rapid destruction of red cells due to an unknown mechanism (milieu hemolysis) [4]. During the course of treatment, chemotherapy causes

myelosuppression which further deranges the already disturbed hemostatic parameters. Laboratory studies almost constantly show marked decreases in red cells and platelets. Therefore, Red cell transfusions are given to maintain hemoglobin level greater than 8.0 g/dl. Platelet transfusions used for hemorrhagic manifestations related to thrombocytopenia and prophylactically if necessary to maintain the platelet count above $10 \times 10^3/\mu\text{l}$ [5]. Clotting abnormalities are managed by transfusion of fresh frozen plasma and cryoprecipitate. Hence, Transfusion support is integral to patient care and substantial amount of blood may be required per patient. However, there is little information about the transfusion requirements of these patients. We undertook this study to evaluate the quantitative aspect of blood component support in newly diagnosed AML patients undergoing chemotherapy. We also documented bleeding outcomes during the course of treatment.

Material and Methods

The study was carried at the Department of Transfusion

Medicine in conjunction with Department of Hematology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, over a period of 18 months. The study was approved by Institutional ethical committee. Of total 175 new patients were diagnosed as AML during the study period, 54 opted for chemotherapy. Only 19 of these patients were enrolled in study. Patients were excluded from the study if they had acute promyelocytic leukemia, secondary AML, if they had received a blood transfusion before the diagnosis of AML, or if they declined to participate.

Patient details

Patient particulars noted included registration number, age, gender, height, weight, ABO and Rh blood group, diagnosis including FAB subtype and phase of chemotherapy. Clinical details such as presence of fever, infection/sepsis, splenomegaly and medications including chemotherapeutic agents (AMB, G-CSF, tranexamic acid) were also noted. Complete blood counts (CBC) were done every morning.

Treatment regimen

Standard treatment regimen during induction included Daunorubicin (60-90mg /m²) for 3 days and cytarabine (100-200mg/m²) for 7 days. High dose cytarabine (1.5-3g/m²) was used for consolidation which was given every 12 hourly for day 1, 3 and 5. All patients who received treatment were followed up till complete remission, relapse, and resistance to chemotherapy or death whichever was earlier.

Transfusion support

Transfusion support given to patients was in form of Leuco Poor Red Blood Cells (LPRBC), Random Donor Platelets (RDP) prepared from whole blood (by Buffy-coat method) or Single Donor Platelets (SDP) and Fresh Frozen Plasma (FFP). RBC transfusions were given for Hb levels ≤ 8 g/dl or for symptomatic anemia. RDP/SDPs were transfused therapeutically in the presence of thrombocytopenic bleed and prophylactically when platelet count was $\leq 10 \times 10^3/\mu\text{l}$ or $10-20 \times 10^3/\mu\text{l}$ in the presence of risk factors such as fever, chemotherapy etc. Transfusion details recorded included component being administered, indication, trigger and number/dose of components transfused. Post transfusion samples were collected for determination of Hb and platelet counts. For monitoring efficacy of platelet transfusion, the post transfusion platelet counts were done both at 1 and 24 hours based on which Corrected Count Increment (CCI) was calculated.

Bleeding data

Patients were assessed daily for bleeding events by patient interview and physical examination. Results were reported using a modified WHO scale for bleeding [6]. *Grade 0*: no bleeding. *Grade 1*: Mild petechiae, ecchymosis and epistaxis/oral bleeding or occult blood loss. *Grade 2*: Moderate bleeds not requiring RBC transfusion e.g. large petechiae, ecchymosis, epistaxis, vaginal bleeding, mild hematemesis, melena, mild hematuria. *Grade 3*: Hemorrhage resulting in rapid decrease of HCT, necessitating RBC transfusions or failure to obtain a post transfusion increment. *Grade 4*: Hemorrhage resulting in severe hemodynamic compromise or bleeding into a vital organ (e.g. intracranial hemorrhage).

Statistical analysis and data management was done using SPSS

statistical computer software (version 13.0, USA). Comparison between two groups were made using χ^2 test for proportions. A 2-sided *p* value < 0.05 was considered significant.

Results

All study patients were followed for 32 chemotherapy cycles which included 19 inductions, 3 reinductions and 10 consolidation chemotherapy. The patient details are summarized in the Table 1. Mean duration of stay per chemotherapy cycle was 23.7(range 3-53) days while for entire treatment the mean duration of hospitalization was 68.5 (range 22-146) days.

Blood/component usage

During the period of hospitalization, overall usages of all components are shown in Table 2.

Red cell transfusions

Seventy percent (186) of the LPRBC were transfused during induction. Mean units transfused during induction was 9.8 vs. 8 units during consolidation (as 19 patients underwent induction whereas only 10 received consolidation chemotherapy cycles). Majority (51.9%) of the LPRBCs used were for management of hemorrhage.

Platelet transfusions

Total of 1050 RDP and 4 SDP were transfused during induction and 500 RDP and 1 SDP were transfused for consolidation chemotherapy. The mean dose of the platelet transfused was similar

Table 1: Patient characteristics.

No. of patients = 19		
Male	15 (79%)	
Female	4 (21%)	
Median age (range)	33 (1 – 58) years	
FAB Subtype		
M1	2	10.5%
M2	13	68.4%
M4	3	15.8%
MPAL	1	5.3%
Baseline variables		
Hb (g/dl)	6.8 \pm 1.43	4.0-8.9
TLC ($\times 10^3/\mu\text{L}$)	54.8 \pm 51.1	1.5-166
Platelet count ($\times 10^3/\mu\text{L}$)	35.1 \pm 14.5	12-61
Blood group distribution of patients		
O (%)	6 (31.6)	
A (%)	7 (36.8)	
B (%)	6 (31.6)	

Table 2: Blood components transfused during the study period.

	No of units	No of transfusion episodes	Mean per patient	Range
LPRBC	266	204	14	3-25
RDP	1550	426	81.6	20-172
SDP	5	5	0.3	0-3
FFP	189	44	10	0-68
Cryoprecipitate	11	2	0.6	0-7

Table 3: Factors associated with inadequate CCI.

Variables (total days of exposure)	CCI at 1 hour(n=426)			CCI at 24 hours (n=426)		
	CCI <7500	CCI >7500	P value	CCI < 4500	CCI > 4500	P value
Fever (n=138)	92	46	<0.05	111	27	<0.05
Infection/sepsis (n=134)	76	58	<0.05	105	29	<0.05
Splenomegaly (n=73)	48	25	<0.05	60	13	<0.05
Daunorubicin (n=19)	17	2	<0.05	18	1	<0.05
Cytarabine (n=62)	49	13	<0.05	56	6	<0.05
Amphotericin B (n=291)	189	102	<0.05	229	62	<0.05

Table 4: Sites of bleeding.

Site of bleeding	Bleeding days (n=256)	%
Gastro-intestinal	73	28.5
Oropharyngeal	49	19.1
Epistaxis	44	17.2
Mucocutaneous	42	16.4
Genitourinary	37	14.5
Invasive site	4	1.6
Others	7	2.7

in both phases of chemotherapy (1.6×10^{11}). A total 711 (45.8%) units of RDP and 4 SDP were transfused prophylactically on 205 instances, with a mean dosage of 1.5×10^{11} platelets per episode. The mean pre transfusion platelet count at which platelet transfusion was given was $13.0 \times 10^3/\mu\text{l}$. Response to platelet transfusion was inadequate (CCI <4500 at 24 hours) in 255 (60%) episodes. All 19 patients were found to be refractory (24 hours CCI < 4500 for 2 or more consecutive transfusions) at some point of time during the treatment. Presence of fever, infection/sepsis, splenomegaly, use of Daunorubicin, Cytarabine and Amphotericin B were found to significantly associated with poor platelet recovery both at 1 and 24 hours ($p < 0.05$ in all factors) (table 3).

FFP transfusion

Of the total 189 units of FFP transfused during the treatment, 175 units were transfused during induction chemotherapy for 40 episodes, while during consolidation chemotherapy 14 units were transfused for 4 episodes. Mean FFP transfused per patient was 8.42 during induction and 1.4 units during consolidation.

Bleeding data

Bleeding was noted on 256 (19.7%) patient days of total 1302 patient days, which included grade 1 bleeding on 115 (8.8%) days, grade 2 on 86 (6.6%) days and grade 3 on 55(4.2%) days. No grade 4 or fatal bleed was noted. Gastro-intestinal and oropharyngeal were most common bleeding sites Table 4. Morning platelet counts on bleeding days are shown in figure 1. Most (133 patient days, 52%) of the bleeding were observed when platelet count was between $10-20 \times 10^3/\mu\text{l}$. As evident from table 5 presence of fever, infection/sepsis and use of Amphotericin B and Tranexamic acid were found to be significantly associated with bleeding ($p < 0.05$).

Discussion

Understanding transfusion needs of AML patients is crucial for

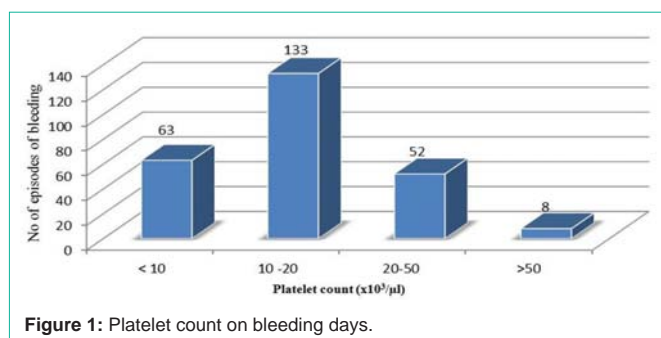


Figure 1: Platelet count on bleeding days.

the appropriate management and planning of health care strategies. Our study sheds light on transfusion requirements for newly diagnosed AML patients undergoing chemotherapy. The mean LRBC usage per patient was 14 units (range 3-25) throughout the hospital stay. Favre *et al.* evaluated transfusion requirements in patients undergoing initial induction consolidation chemotherapy for newly diagnosed AML. The group reported a median usage of 18 RBC units (range 3-44) during the course of chemotherapy [7]. In the present study the mean RBC requirement during the induction phase was higher than during the subsequent consolidation phase (9.8 vs. 8). The same pattern of RBC usage was also found in studies by Dawson *et al.* and Favre *et al.* who reported that the mean RBC requirement was higher during initial phase of induction chemotherapy [7,8].

During the chemotherapy, mean number of RDP units (55.3 units during induction vs. 50 during consolidation) and thus the dose of transfused platelets was not significantly different during the induction and consolidation phases. The usage pattern as reported by Dawson *et al.* [8] was, 12 platelet units which were transfused during induction and 7 and 9 platelet units during subsequent consolidation phases for 111 AML patients undergoing chemotherapy while Favre *et al.* [7] reported median usage of 6 platelet units during first induction and 4 platelet units in the second induction and during consolidation the median usage was 2 and 4 platelet units in subsequent consolidation phase of chemotherapy. In current study mean dosage of 3.6 RDP units (1.6×10^{11} platelets) per transfusion episode was administered, while in studies by Dawson *et al.*[8] and Favre *et al.*[7] dosage of the platelet being used was 2×10^{11} platelets per transfusion derived from 4-5 pools of whole blood derived platelets or a single apheresis units.

The mean platelet dose transfused in our study was ($\sim 1.6 \times 10^{11}$ platelets) which was equivalent to the low dose category as reported by Tinmouth *et al.* [10] (3 whole blood derived platelets, WBDP) and Slichter *et al.* [9] (1.1×10^{11} platelets/ m^2). (3 whole blood

Table 5: Factors associated with risk of bleeding.

Variables (total days of exposure)	Days of transfusion with Bleeding	Days of transfusion without bleeding	P value
Fever (n=166)	104	62	<0.05
Infection/sepsis (n=151)	85	66	<0.05
Splenomegaly (n=76)	37	39	0.89
Daunorubicin (n=24)	14	10	0.37
Cytarabine (n=82)	39	43	0.69
Amphotericin B (n=307)	183	124	<0.05
G-CSF (n=316)	154	162	0.69
Tranexamic acid (n=343)	193	150	<0.05

derived platelets, WBDP). Tinmouth *et al.* studied the safety and effectiveness of low dose (3 WBDP) vs. high dose platelets (5 WBDP) in acute leukemics and recipients of autologous stem cell transplant. He reported that the patients who were transfused with low dose prophylactic platelets received 25% fewer platelets thus, favoring the use low dose platelet transfusion which appeared to be safe and effective [10]. Slichter *et al.* compared three different platelet doses in hypoproliferative thrombocytopenia and reported that the use of low dose (1.1×10^{11} platelets/m²) platelet transfusion led to decreased usage of platelets. The low dose platelet transfusions were also found to be effective without any adverse events [9]. Recently in an another large randomized multicentre trial comparing the traditional prophylactic platelet transfusion strategy with a therapeutic transfusion strategy in patients with acute myeloid leukaemia or autologous haematopoietic stem-cell transplantation. Investigators recommended restrictive platelet transfusion strategy than is presently used worldwide in non-bleeding and clinically stable patients despite a morning platelet count of less than $10 \times 10^3/\mu\text{l}$ [11].

The response to platelet transfusion was inadequate in 60% episodes. Friedberg *et al.* [12] evaluated clinical and blood bank factors or management of platelet refractoriness and alloimmunization in haemato-oncology patients. They reported CCI <5000 in 50.2% of platelet transfusions. In the current study, presence of fever, infection/sepsis, splenomegaly, and use of Daunorubicin, cytarabine and Amphotericin B were significantly associated with poor CCI both at 1 hour and 24 hours. Bishop *et al.* [13] has reported significant correlation between splenomegaly, administration of AMB and poor CCI at both 1 hour and 24 hour, with other factors marginally affecting the CCI. Similar findings have also been reported by Friedmann *et al.* [14] where he found clinical factors such as fever, bleeding, DIC, sepsis, splenomegaly, neutropenia to affect the response to platelet transfusions. Slichter *et al.* [15] has also reported that the presence of palpable spleen, bleeding, fever, infection and use of amphotericin B negatively affects the platelet increment at 1 hour and 24 hour.

All 19 patients in our study were refractory to platelet transfusions at some point of time during the treatment, the increased rate of refractoriness in our study could be largely due to the use of ABO incompatible and non leukofiltered platelets. Fever, infection/sepsis, splenomegaly, and use of Daunorubicin, cytarabine and Amphotericin B also have contributed to refractoriness. Unfortunately, the humoral causes of platelet refractoriness e.g. HLA or HPA antibodies were not evaluated.

Mean FFP units transfused per patient was 10 (range 0-68). Majority of which were (92.6%) transfused during the induction phase while cryoprecipitate was required only on two instances. We could not find any study quantifying FFP/Cryoprecipitate usage in patients of AML (excluding APML).

We observed clinically significant bleeding (grade ≥ 2) on 141 days (10.8%) and severe bleeding on 55 days (4.2%). Webert *et al.* has also reported total of 743 (10.13%) days of bleeding over 7335 patient-days. They found 560 days (75.4%) days with grade 1, 108 (14.5%) days with grade 2, 51 (6.9%) with grade 3 and 24 (3.2%) with grade 4 bleeding severity [16]. Heddle *et al.* [17] reported clinically significant bleeding on 12.1% patient days and fatal bleed on 0.5 % days of observation with low dose prophylactic transfusion (corresponding to

a dose of $1.5-3 \times 10^{11}$ platelet per transfusion). Similarly in an another multicentre trial, Heddle *et al.* [18] observed 6% days with clinically significant bleed (\geq Grade 2) of the total patient days observed when platelets were transfused prophylactically at a trigger of $10 \times 10^3/\mu\text{l}$ (centre: Italy). Thus, severity of the bleeding observed in our study was concordant to other studies. Bleeding from gastrointestinal tract was most frequent in our study present on 28.5% of bleeding days. This was closely followed by oropharyngeal bleeding which was seen on 19.1% bleeding days. Rebullia *et al.* evaluated the sites of major of major bleeding (\geq WHO grade 2) and observed that most common site of bleeding was gastrointestinal tract (23.6%) [19].

Sixty-three (24.6%) bleeding episodes were observed with platelet count $< 10 \times 10^3/\mu\text{l}$ and 133 (52%) when the platelet count was $10-20 \times 10^3/\mu\text{l}$ while 52 (20.3 %) episodes of bleeding occurred when platelet count was $20-50 \times 10^3/\mu\text{l}$, and 8 (3.1 %) when platelet count was $> 50 \times 10^3/\mu\text{l}$. We noted that majority of bleeding episodes (76.6%) occurred when the platelet count was less than $20 \times 10^3/\mu\text{l}$. This is in corroboration of study by Lawrence *et al.* [20] who while studying relationship between platelet count and presence of major or minor bleed, observed close correlation between lower platelet counts ($< 10 \times 10^3/\mu\text{l}$) and minor bleeding. A similar relation was also observed for major bleeding. However, majority of their bleeding episodes (50%) were reported when the counts were $< 5 \times 10^3/\mu\text{l}$. This is in contrast to our study where majority of bleeding episodes occurred at $10-20 \times 10^3/\mu\text{l}$ (52%) This could be attributed to the fact that our patients received prophylactic platelet transfusions at counts $< 10 \times 10^3/\mu\text{l}$. The difference in the platelet counts at which bleeding occurred was also influenced by the presence of other associated risk factors that led to bleeding. In our study, presence of fever, infection/sepsis and use of Amphotericin B and Tranexamic acid were found to be significantly associated with bleeding. Presence of various factors associated with bleeding has also been investigated in a study by Friedmann *et al.* [14] where he found that neither the first morning platelet count nor the lowest platelet count of the day were significantly related to the risk of bleeding. He also reported a correlation between bleeding and presence of fever (OR-1.21), bacteraemia (OR-1.06) and use of Amphotericin B (OR-1.62). Tranexamic acid is mainly used as a supportive therapy in bleeding patients thus, its use was associated with presence of bleeding [21].

Blood transfusion support remains an indispensable part of the patient undergoing chemotherapy as substantial number of RBC, platelets and FFP are required during course of treatment. Our findings indicate that the threshold of $20 \times 10^3/\mu\text{l}$ for prophylactic platelet transfusion is safe for AML patients who are not actively bleeding or not high risk. In cases where additional risk factors are present the threshold should be increased up to $20 \times 10^3/\mu\text{l}$ and in the presence of major bleeding complications the platelets count should be maintained greater than $20 \times 10^3/\mu\text{l}$. In conclusion the study provided insights into the complex issues of transfusion requirement of AML patients. We emphasize individualizing transfusion management of these patients as clinical factors are the major determinants of transfusion requirements. We also recommend that bleeding grades should be used as an outcome measure when determining the efficacy of platelet transfusions.

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