Research Article

Defining Current Patterns of Blood Product Use during Intensive Induction Chemotherapy in Newly Diagnosed Acute Myeloid Leukemia Patients

Liron Miller[a]   Mor Freed-Freundlich[b]   Avichai Shimoni[b]   Tamer Hellou[b]
Abraham Avigdor[b]   Mudi Misgav[a]   Jonathan Canaani[b]

[a]Blood Bank and Transfusion Service, Chaim Sheba Medical Center, Faculty of Medicine, Tel Aviv University, Tel Hashomer, Israel; [b]Hematology Division, Chaim Sheba Medical Center, Faculty of Medicine, Tel Aviv University, Tel Hashomer, Israel

Abstract

Introduction: Blood product transfusion retains a critical role in the supportive care of patients with acute myeloid leukemia (AML). Whereas previous studies have shown increased transfusion dependency to portend inferior outcome, predictive factors of an increased transfusion burden and the prognostic impact of transfusion support have not been assessed recently. *Methods/Patients:* We performed a retrospective analysis on a recent cohort of patients given intensive induction chemotherapy in 2014–2022. *Results:* The analysis comprised 180 patients with a median age of 57 years with 80% designated as de novo AML. Fifty-four patients (31%) were *FLT3-ITD* mutated, and 73 patients (42%) harbored *NPM1*. Favorable risk and intermediate risk ELN 2017 patients accounted for 43% and 34% of patients, respectively. The median number of red blood cell (RBC) and platelet units given during induction were 9 and 7 units, respectively. Seventeen patients (9%) received cryoprecipitate, and fresh frozen plasma (FFP) was given to 12 patients (7%). Lower initial hemoglobin and platelet levels were predictive of increased use of RBC ($p < 0.0001$) and platelet transfusions ($p < 0.0001$). FFP was significantly associated with induction related mortality (42% vs. 5%; $p < 0.0001$) and with *FLT3-ITD* (72% vs. 28%; $p = 0.004$). Blood group AB experienced improved mean overall survival compared to blood group O patients (4.1 years vs. 2.8 years; $p = 0.025$). In multivariate analysis, increased number of FFP (hazard ratio [HR], 4.23; 95% confidence interval [CI], 2.1–8.6; $p < 0.001$) and RBC units (HR, 1.8; 95% CI, 1.2–2.8; $p = 0.008$) given was associated with inferior survival. *Conclusion:* Transfusion needs during induction crucially impact the clinical trajectory of AML patients.

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Introduction

With the panoply of recently approved agents targeting various biological facets of the leukemic clone, the field of acute myeloid leukemia (AML) is experiencing a much-awaited upsurge indicative of improving outcomes for patients with this often-lethal hematologic malignancy [1–7]. Yet, despite these meritorious therapeutic

Correspondence to:
Jonathan Canaani, Jonathan.canaani@sheba.health.gov.il

advances, supportive care, in the form of infection control and blood product transfusion, remains a crucial cornerstone of management of AML patients, particularly during the initial precarious phase of diagnosis and induction chemotherapy. Indeed, AML patients will require over the course of their disease substantial blood product support with red blood cell (RBC) and platelet transfusions, and occasionally also fresh frozen plasma (FFP) [8, 9]. Point of fact, it has been estimated that over 25% of transfused platelet infusions are used in the setting of acute leukemia [10, 11]; moreover, previous studies have demonstrated the profound clinical impact associated with transfusion dependency on survival of AML patients, receiving intensive induction chemotherapy and the tight association between transfusion burden and response to therapy [12–14]. While administration of blood products is guided by societal recommendations [15], there exists a substantial variability among physicians taking care of AML patients resulting in widely differing transfusion practices [16]. Consequently, as one considers the pivotal role of transfusion in the management of AML patients, it is of prime importance to provide a current assessment of the clinical impact of the transfusion burden during initial induction chemotherapy and delineate thoroughly possible associations between baseline clinical, cytogenetic, and molecular features of the disease and the incurring transfusion intensity whose impact extends also to health care planning strategies and incurring health care costs [17]. In this analysis of a recently treated AML patient cohort, we provide contemporary data on transfusion requirements of all blood products including FFP and cryoprecipitate and reveal clinically significant associations between baseline clinical, blood group, and molecular parameters with overall survival, achievement of remission, risk of major bleeding, and risk of transfusion-associated alloimmunization.

Patients and Methods

Study Cohort and Definitions

We reviewed the medical records of 180 consecutive adult patients with newly diagnosed AML, who were treated with intensive chemotherapy from December 2014 through January 2022 at the Sheba Medical Center. Clinical data extraction and exploration were done with the MDClone big data platform. All patients assessed in the study received standard anthracycline (daunorubicin, 60 mg/m^2; days 1–3) and cytarabine-based (100 mg/m^2; continuous infusion days 1–7) intensive induction chemotherapy or CPX-351 (100 units/m^2 on days 1, 3, 5). Patients who did not respond to the initial induction cycle were given a second induction course consisting of intravenous mitoxantrone at

a dose of 20 mg/m^2 on days 1–2 and high-dose cytarabine at a dose of 3 g/m^2 intravenously on days 1–5 [18]. AML was defined according to criteria established by the World Health Organization [19]; patients with a prior history of myelodysplastic syndromes or a myeloproliferative neoplasm or those treated with prior chemotherapy for a different malignancy were classified as secondary AML. Cytogenetic risk was assessed according to the recommendations of the modified UK Medical Research Council (MRC) [20], whereas the 2017 European LeukemiaNet (ELN 2017) was used for determination of overall disease risk [21]. Patients with acute promyelocytic leukemia were excluded from this study. For the purposes of this analysis, a major bleeding event was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome or bleeding causing a fall in hemoglobin level of 2 g/dL or more or leading to transfusion of two or more units of whole blood or red cells [22]. Induction mortality was defined as any death occurring within 30 days of administration of induction chemotherapy. Single donor platelets were collected by apheresis as previously described [23]. All patients received irradiated and leukodepleted blood products [24]. Pre-storage leukodepletion of RBC units was performed in blood donations collected locally at our institute's blood bank, whereas RBC units procured from the Israeli national blood service were not pre-storage leukodepleted. The additive solutions used for RBC storage were CPDA-1 and SAGM, and the maximum allowed storage time for red cell concentrates was 35 days. Platelet concentrates were stored in plasma. Transfusion triggers for RBC transfusion and platelet transfusion were 8 g/dL and 10×10^9/L, respectively [16]. Patients experiencing active bleeding or those planned for an invasive procedure with a high risk of bleeding were given FFP and/or cryoprecipitate per treating physician's choice. Alloimmunization was defined according to the National Heart, Lung, and Blood Institute Working Group criteria [25]. The Institutional Review Board of the Chaim Sheba Medical Center approved this study.

Statistical Analysis

Commensurate with established criteria, a complete remission (CR) was defined as identification of less than 5% blasts in a bone marrow study parallel to blood count recovery, namely, a neutrophil count of $\geq1,000$/μL and a platelet count of $\geq100,000$/μL. CR with incomplete count recovery was defined as fulfilling all CR criteria except for an absolute neutrophil count <1,000/μL or a platelet count <100,000/μL [26]. Patients were designated as refractory to induction chemotherapy if they did not achieve CR/incomplete count recovery after 2 courses of intensive induction chemotherapy [21]. Overall survival was calculated from the initial day of diagnosis to death from any cause or to time of last follow-up [27]. Nominal data were compared using the Fisher's exact test or Pearson's χ^2 test. Continuous variables were compared with one-way analysis of variance (ANOVA) with post hoc analysis with the Tukey's b test. The Pearson correlation methodology was used to estimate the association between continuous variables. Multivariable regression analysis using Cox-Snell R^2 was conducted by including all variables in univariate analyses with $p < 0.1$ and then using backward stepwise elimination to obtain the final model with only the significant ($p < 0.05$) independent variables. Covariates included in the multivariate analysis were patient age, WBC count at diagnosis, disease type (de novo vs. secondary),

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Table 1. Baseline features of 180 newly diagnosed AML patients who underwent intensive induction chemotherapy

Clinical parameter	Entire cohort (N = 180)
Year of diagnosis, median (range)	2018 (2014–2022)
Patient age in y, median (range)	57 (19–77)
Gender, n (%)	
Male	87 (48)
Female	93 (52)
WBC at diagnosis (×10^9/L), median (range)	9.2 (0.1–294)
Hemoglobin at diagnosis, g/dL, median (range)	9.1 (4.4–14.8)
Platelets at diagnosis (×109/L), median (range)	63 (5–308)
Creatinine, mg/dL, median (range)	0.75 (0.4–10.7)
Uric acid, mg/dL, median (range)	4.8 (1.1–14.7)
LDH, IU, median (range)	393 (122–3,302)
Leukemia type, n (%)	
De novo	144 (80)
Secondary	36 (20)
FLT3-ITD status, n (%)	
Wild type	121 (69)
Mutated	54 (31)
Missing	5
NPM1 status, n (%)	
Wild type	99 (58)
Mutated	73 (42)
Missing	8
MRC cytogenetic risk category, n (%)	
Favorable	19 (11)
Intermediate	109 (61)
Adverse	36 (20)
Insufficient	15 (8)
Missing	1
ELN 2017 risk category, n (%)	
Favorable	77 (43)
Intermediate	62 (34)
Adverse	41 (23)
Clinical outcome, n (%)	
Remission	144 (80)
Induction death	13 (7)
Refractory	23 (13)
ICU admission during induction	9 (5)
Major bleeding event	7 (4)

FLT3-ITD, *NPM1*, blood group type, MRC risk category, RBC, platelet, and FFP transfusions. All tests were two sided, and a *p* value < 0.05 was considered statistically significant. Analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline Features and Clinical Outcomes of the Study Population

Our study cohort consisted of 180 patients diagnosed and treated at our institution between the years 2014 and 2022 with a median follow-up duration of 15.9 months (range 0.2–85.6 months). Median patient age at diagnosis was 57 years (range 19–77 years) with a slight female predominance (52%). As outlined in Table 1, the median WBC count at diagnosis was 9.2×10^9/L (range 0.1–294), and the median platelet count was 63×10^9/L (range 9–308). Hundred and forty-four patients (80%) were designated as de novo AML, while the remainders were designated as secondary disease. The *FLT3-ITD* mutation was detected in 54 patients (31%), whereas 73 patients (42%) were found to be *NPM1* mutated. Of 62 patients assessed for biallelic mutated *CEBPA*, only 1

Table 2. Transfusion-related data

Clinical parameter	Entire cohort ($N = 180$)
Patient blood type	
A	67 (37)
AB	16 (9)
B	38 (21)
O	59 (33)
Rh status	
Negative	19 (11)
Positive	161 (89)
30-d number of total RBC units given, median (range)	9 (0–30)
30-d number of pre-storage leukodepleted RBC units given, median (range)	1 (0–16)
30-d number of total platelet units given, median (range)	6.5 (2–60)
30-d number of SDP units given, median (range)	4 (0–43)
30-d number of FFP units given, median (range)	0 (0–9)
Cryoprecipitate given during induction	
No	163 (91)
Yes	17 (9)
Alloimmunization	
No	173 (96)
Yes	7 (4)

RBC, red blood cells; FFP, fresh frozen plasma; Rh, Rhesus factor.

patient (1.6%) was found to harbor the mutation. In terms of risk stratification data, 19 patients (11%) harbored favorable risk MRC cytogenetic studies at diagnosis, while intermediate risk and adverse risk karyotypic studies were seen in 109 patients (61%) and 36 patients (20%), respectively. Most of the patients on the study cohort were assessed as either favorable risk ELN 2017 (77 patients, 43%) or intermediate risk ELN 2017 (62 patients, 34%). During the index admission for induction chemotherapy, 9 patients (5%) were admitted to the intensive care unit (ICU), and 7 patients (4%) experienced a major bleeding event.

Following receipt of intensive induction chemotherapy, 144 patients (80%) achieved remission, 23 patients (13%) were refractory to therapy, and 13 patients (7%) experienced early induction death. The 2-year overall survival rate is estimated at 56% with a relapse rate of 34.4%. 123 patients (68%) were referred to an allogeneic stem cell transplantation.

Blood Banking-Associated Characteristics

Table 2 summarizes the transfusion-related data of the analyzed cohort. Blood group types A and O were the most common blood groups of patients analyzed, seen in 67 patients (37%) and 59 patients (33%), respectively. The median number of 30-day RBC units given was 9 (range 0–30) with a median number of pre-storage leukodepleted RBC units of 1 (range 0–16) during the same time period. In terms of receipt of platelet units, the median number of 30-day total platelet units given was 7 (range 2–60) with a median number of single donor platelet (SDP) units of 4 (range 0–43). Cryoprecipitate was given to 17 patients (9%). Transfusion-related alloimmunization occurred in 7 patients (4%).

Comparison of Clinical Parameters in AML Patients Stratified by RBC Transfusion Requirements

To assess whether baseline clinical and disease-related parameters differed to a significant degree among AML patients according to the number of RBC transfusions given during induction, we performed a univariate analysis which is outlined in Table 3. Groups were dichotomized based on the median number of RBC transfusions received during the initial 30 days of hospitalization. Patients with lower initial hemoglobin levels were more likely to receive more than 10 RBC units compared with patients presenting with higher hemoglobin levels (8.3 g/dL vs. 9.9 g/dL; $p < 0.0001$). A similar observation was also noted for patients presenting with a lower initial platelet count (59×10^9/L vs. 92×10^9/L; $p = 0.001$). In addition, serum uric acid levels and LDH levels were significantly higher at initial presentation in patients

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Table 3. Comparison of disease and transfusion-related characteristics among AML patients according to RBC requirements during induction

Clinical parameter	Total RBC units ≤10 (N = 122)	Total RBC units >10 (N = 58)	p value
WBC level at diagnosis (×10^9/L), mean (SE mean)	31.1 (4.9)	38.1 (5.7)	0.39
Hemoglobin level at diagnosis, g/dL, mean (SE mean)	9.9 (0.17)	8.3 (0.2)	<0.0001
Platelet level at diagnosis (×10^9/L), mean (SE mean)	92 (5.8)	59 (7.3)	0.001
LDH level, log at diagnosis, mean (SE mean)	5.9 (0.06)	6.2 (0.08)	0.004
Uric acid level, log at diagnosis, mean (SE mean)	1.5 (0.03)	1.6 (0.06)	0.031
30-d total SDP units given, mean (SE mean)	4.6 (0.31)	9.1 (1.03)	<0.0001
30-d total platelet units given, mean (SE mean)	6.8 (0.4)	14.9 (1.5)	<0.0001
30-d total FFP units given, mean (SE mean)	0.11 (0.05)	0.54 (0.2)	0.058

Clinical parameter	Pre-storage leukodepleted RBC units = 0 (N = 81)	Pre-storage leukodepleted RBC units ≥1 (N = 99)	p value
WBC level at diagnosis (×10^9/L), mean (SE mean)	30.9 (5.6)	35.3 (5.2)	0.56
Hemoglobin level at diagnosis, g/dL, mean (SE mean)	9.4 (0.2)	9.3 (0.2)	0.8
Platelet level at diagnosis (×10^9/L), mean (SE mean)	93 (7.4)	72 (5.9)	0.025
LDH level, log at diagnosis, mean (SE mean)	5.8 (0.07)	6.1 (0.06)	0.004
Uric acid level, log at diagnosis, mean (SE mean)	1.4 (0.04)	1.62 (0.04)	0.035
30-d total SDP units given, mean (SE mean)	4.9 (0.39)	6.9 (0.69)	0.022
30-d total platelet units given, mean (SE mean)	7.9 (0.6)	10.7 (1.07)	0.029
30 d total FFP units given, mean (SE mean)	0.19 (0.09)	0.3 (0.12)	0.49

with a higher RBC transfusion burden (1.6 vs. 1.5; $p = 0.031$ and 6.2 vs. 5.9; $p = 0.004$, respectively; logarithmic transformation). We also observed a significant association between receipt of more than 10 RBC units and an increased number of transfusions of total platelet units (14.9 vs. 6.8; $p < 0.0001$) as well as SDP infusions (9.1 vs. 4.6; $p < 0.0001$). There was a near-statistical trend indicating that the group of patients receiving more than 10 RBC units was also given more FFP units (0.54 vs. 0.11; $p = 0.058$). We proceeded to perform an additional analysis focusing specifically on the use of pre-storage leukodepleted RBC which was received by 99 patients (55% of the patient cohort). As shown in Table 3, diverging from the previous observation, there was no significant difference in the use of pre-storage leukodepleted RBC units in terms of baseline hemoglobin level and the use of FFP units. In line with the previous observations, patients who received pre-storage leukodepleted RBC units had lower initial platelet counts, higher initial uric acid and LDH levels, and were more likely to receive more platelet units as well as more SDP units. We could not establish a statistically significant association between increased use of total RBC units and pre-storage leukodepleted RBC units and patient blood group type, disease type (de novo vs. secondary AML), MRC cytogenetic risk group, molecular profile, and ELN 2017 risk group.

Comparison of Clinical Parameters in AML Patients Stratified by Platelet Transfusion Requirements

As shown in Table 4, we performed a univariate analysis comparing patients who received more or less than 6 platelet units during their index admission for induction chemotherapy. Patients with lower initial hemoglobin values (9.1 g/dL vs. 9.7 g/dL; $p = 0.049$) and platelet counts (50×10^9/L vs. 112×10^9/L; $p < 0.001$) were more likely to receive more than 6 platelet units. Additionally, the group of patients receiving more than 6 platelet units was characterized by significantly higher baseline LDH levels (6.2 vs. 5.8; $p < 0.0001$, logarithmic transformation) and increased need for FFP (0.47 units vs. 0.02 units; $p = 0.005$) and cryoprecipitate (14% vs. 4%; $p = 0.039$) infusions. A similar analysis focusing on the patient subset who received SDP infusions also revealed that patients receiving more than 3 SDP units were more likely to have lower initial hemoglobin (9.1 g/dL vs. 9.9 g/dL; $p = 0.006$) and platelet levels (65 vs. 108; $p < 0.0001$) as well as increased use of FFP units (0.36 units vs. 0.06 units; $p = 0.032$). Furthermore, the group of patients receiving more than 3 SDP units was notable for a significantly increased likelihood of admission to the ICU compared with the group receiving less than 3 SDP units (8% vs. 0%; $p = 0.027$). Distribution of blood type groups also

Table 4. Comparison of disease and transfusion-related characteristics among AML patients according to platelet transfusion requirements during induction

Clinical Parameter	Total platelet units ≤6 (N = 90)	Total platelet units >6 (N = 90)	p value
WBC level at diagnosis (×10^9/L), mean (SE mean)	28.5 (5.5)	38.1 (5.3)	0.21
Hemoglobin level at diagnosis, g/dL, mean (SE mean)	9.7 (0.22)	9.1 (0.2)	0.049
Platelet level at diagnosis (×10^9/L), mean (SE mean)	112 (6.7)	50 (4.7)	<0.0001
LDH level, log at diagnosis, mean (SE mean)	5.8 (0.06)	6.2 (0.07)	0.0001
Uric acid level, log at diagnosis, mean (SE mean)	1.5 (0.04)	1.6 (0.04)	0.13
30-d total filtered RBC units, mean (SE mean)	1.5 (0.23)	2.1 (0.35)	0.17
30-d total FFP units given, mean (SE mean)	0.02 (0.02)	0.47 (0.15)	0.005
Cryoprecipitate infusion given, n (%)	4 (4)	13 (14)	0.039

Clinical parameter	SDP units ≤3 (N = 67)	SDP units >3 (N = 113)	p value
WBC level at diagnosis (×10^9/L), mean (SE mean)	25.5 (5.5)	38 (5.1)	0.11
Hemoglobin level at diagnosis, g/dL, mean (SE mean)	9.9 (0.26)	9.1 (0.17)	0.006
Platelet level at diagnosis (×10^9/L), mean (SE mean)	108 (7.5)	65 (5.5)	<0.0001
LDH level, log at diagnosis, mean (SE mean)	5.7 (0.07)	6.2 (0.06)	<0.0001
Uric acid level, log at diagnosis, mean (SE mean)	1.5 (0.04)	1.6 (0.04)	0.19
30-d total filtered RBC units, mean (SE mean)	1.3 (0.2)	2.1 (0.3)	0.091
30-d total FFP units given, mean (SE mean)	0.06 (0.06)	0.36 (0.12)	0.032
Cryoprecipitate infusion given, n (%)	4 (6)	13 (12)	0.29
ICU admission, n (%)	0	9 (8)	0.027

varied significantly with respect to the use of SDP infusions (*p* = 0.035), such that the patient group receiving less than 3 SDP units comprised 11 AB blood type patients (16%) and 11 B blood type patients (16%), while in the patient group receiving more than 3 SDP units, there were 5 AB blood type patients (4%) and 27 B blood type patients (24%). No significant association was found between increased use of platelet infusions and SDP infusions and disease type, MRC cytogenetic risk group, molecular profile, and ELN 2017 risk group.

Use and Clinical Impact of Fresh Frozen Plasma and Cryoprecipitate during Induction Chemotherapy

The vast majority of patients in this analysis were not given FFP units during their admission for induction chemotherapy. Table 5 outlines a univariate analysis comparing the clinical features of the 12 patients (7%) who did receive FFP infusions with the 167 patients who did not receive FFP. Patients receiving FFP were more likely to have an increased WBC count at diagnosis (70.4 × 10^9/L vs. 30.5 × 10^9/L; *p* = 0.009) as well as lower initial platelet count (41 × 10^9/L vs. 84 × 10^9/L; *p* = 0.0001). Compared with patients who did not receive FFP, patients given FFP were given more platelet infusions (18.2 vs. 8.8; *p* = 0.0003) whereas receipt of SDP units was not significantly different between groups (*p* = 0.107). In terms of clinical outcomes,

compared with their counterparts, patients receiving FFP were far less likely to achieve remission following induction chemotherapy (33% vs. 83%; *p* < 0.0001) and experienced a significantly increased rate of induction related mortality (42% vs. 5%; *p* < 0.0001). In addition, the rate of ICU admissions was significantly higher in patients given FFP (25% vs. 4%; *p* = 0.016). With respect to leukemia-related features, the group of patients receiving FFP was characterized by a higher rate of *FLT3-ITD* positivity (72% vs. 28%, *p* = 0.004), and a trend toward statistical significance suggesting FFP receiving patients was less likely to harbor MRC favorable risk cytogenetic studies compared with their counterparts (0% vs. 11%; *p* = 0.074). As shown in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000529595), the group of 17 patients who received cryoprecipitate during their admission for induction chemotherapy was characterized by a higher WBC count at diagnosis concomitant to a lower initial platelet count. Use of RBC infusions, total platelet units given, and SDP units administered did not reach statistical significance. Of note, the group of patients who received cryoprecipitate experienced a significantly higher rate of induction-related mortality compared to the group of patients not receiving cryoprecipitate (24% vs. 6%; *p* = 0.02) and were more likely to harbor the *FLT3-ITD* mutation (65% vs. 27%; *p* = 0.004).

Table 5. Comparison of disease and transfusion-related characteristics among AML patients who required FFP infusions during intensive induction therapy

Clinical parameter	No FFP infusions (N = 168)	Required FFP infusions (N = 12)	p value
WBC at diagnosis (×10⁹/L), mean (SE mean)	30.5 (3.93)	70.4 (14.1)	0.009
Hemoglobin at diagnosis, g/dL, mean (SE mean)	9.4 (0.15)	8.9 (0.56)	0.42
Platelets at diagnosis (×10⁹/L), mean (SE mean)	84 (4.9)	41 (7.8)	0.0001
LDH level at diagnosis, log, mean (SE mean)	6 (0.05)	6.7 (0.21)	0.0003
30-d total SDP units given, mean (SE mean)	5.6 (0.38)	11.2 (3.16)	0.107
30-d total platelet units given, mean (SE mean)	8.8 (0.63)	18.2 (3.5)	0.0003
Induction outcome, n (%)			
Remission	139 (83)	4 (33)	<0.0001
Induction death	8 (5)	5 (42)	
Refractory to induction	20 (12)	3 (25)	
FLT3-ITD			
Wild type	118 (72)	3 (27)	0.004
Mutated	45 (28)	8 (72)	
MRC cytogenetic risk category, n (%)			
Favorable	19 (11)	0	0.074
Intermediate	103 (62)	5 (46)	
Adverse	33 (20)	3 (27)	
Insufficient	12 (7)	3 (27)	
ICU admission, n (%)			
No	161 (96)	9 (75)	0.016
Yes	6 (4)	3 (25)	

Association of Baseline Clinical and Transfusion-Related Data on Risk of Alloimmunization

To investigate a possible association between clinical and transfusion-related characteristics and risk of transfusion-associated alloimmunization, we performed the univariate analysis shown in online supplementary Table 2. In all, 7 patients (4%) experienced subsequent alloimmunization. Patients with lower mean initial platelet counts were more likely to experience alloimmunization (38×10^9/L vs. 83×10^9/L; $p = 0.01$). Alloimmunized patients had significantly higher RBC transfusion (14 units vs. 9.5 units; $p = 0.012$) and filtered RBC (6.1 units vs. 1.6 units; $p < 0.0001$) requirements during induction compared with non-alloimmunized patients. Moreover, the alloimmunized patient subset was given significantly more platelet units (23.5 vs. 8.9; $p < 0.0001$) and SDP units (18.7 vs. 5.5; $p = 0.039$). A complete specification of the antibodies detected in alloimmunized patients is outlined in online supplementary Table 4.

Impact of Transfusion-Related Factors on Clinical Outcome

Table 6 outlines a univariate analysis comparing overall survival and leukemia-free survival according to blood group type and transfusion requirements during induction chemotherapy. As outlined in Figure 1, AB blood group patients experienced the longer mean overall survival compared with blood group O patients who were observed to have significantly inferior survival (4.1 years vs. 2.8 years; $p = 0.025$). The transfusion burden of pre-storage leukodepleted RBC units was significantly associated with overall survival (Fig. 2) to the extent that patients who were not given pre-storage leukodepleted RBC units experienced mean overall survival of 4.1 years compared with patients who were transfused and who had mean overall survival of 3.2 years ($p = 0.04$). As shown in Figure 3, a similar finding was also noted for patients requiring FFP infusions (OS of 0.7 years vs. 3.8 years; $p < 0.0001$).

We then performed a multivariate analysis which confirmed that the number of FFP units given during induction was independently associated with inferior survival (hazard ratio, 4.23; 95% confidence interval [CI], 2.1–8.6; $p < 0.001$). In addition, increased transfusion burden of pre-storage leukodepleted RBC was independently associated with worse overall survival (hazard ratio, 1.8; 95% CI, 1.2–2.8; $p = 0.008$).

There was a statistical trend indicating that increased use of SDP transfusions was associated with an increased

Table 6. Univariate analysis of the impact of transfusion-related factors on clinical outcome of AML patients undergoing intensive induction therapy

Clinical variable	Parameter	Mean OS (95% CI)	Median LFS (95% CI)
Blood type	A	3.8 years (3.1–4.5)	0.8 years (0.6–1.04)
	AB	4.1 years (3.1–5.1)	1.01 years (0.3–1.7)
	B	3.6 years (2.6–4.6)	0.67 years (0.4–0.95)
	O	2.8 years (2–3.6)	0.43 years (0.3–0.6)
	p value	0.025	0.059
Total number of pre-storage leukodepleted RBC units given during 30 d	0	4.1 years (3.4–4.8)	0.95 years (0.6–1.3)
	≥1	3.2 years (2.5–3.9)	0.7 years (0.5–0.9)
	p value	0.04	0.21
Total number of platelets units given during 30 d	≤6 units	3.9 years (3.3–4.6)	1 year (0.7–1.3)
	>6 units	3.3 years (2.6–3.9)	0.67 years (0.4–0.9)
	p value	0.1	0.067
Total pooled donor platelet units given during 30 d	≤1 unit	4.1 years (3.4–4.8)	0.9 years (0.6–1.2)
	>1 unit	3.1 years (2.4–3.7)	0.7 years (0.5–0.9)
	p value	0.076	0.24
FFP units given during 30 d	0 units	3.8 years (3.3–4.3)	0.8 years (0.6–1)
	>0 units	0.7 years (0.2–1.3)	0.05 years (0.05–0.05)
	p value	<0.0001	<0.0001

likelihood of induction-related mortality (10.6% in patients given over 3 units of SDP vs. 1.5% in patients given 3 or less SDP units; $p = 0.076$). In terms of bleeding events during induction, a major bleeding event occurred in 7 patients (4%) and was significantly associated with induction-related mortality (43% in patients with major bleeding vs. 6% in patients without a major bleeding event; $p = 0.001$) and admission to the ICU (29% vs. 4%; $p = 0.041$). Additional bleeding related data are outlined in online supplementary Table 3. The occurrence of a major bleeding event did not reach statistical significance in terms of median overall survival (5.2 months vs. 28 months; $p = 0.4$) and leukemia-free survival (2.6 months vs. 7.9 months; $p = 0.9$).

Discussion

While intensive chemotherapy forms the centerpiece of the treatment paradigm for newly diagnosed presenting with AML, supportive care with transfusion of blood products retains a critical role in assuaging the profound cytopenias characteristic of AML patients during the initial intensive induction phase of therapy. In this analysis of 180 newly diagnosed patients treated with intensive induction chemotherapy, we thoroughly dissected the various blood product components administered during induction aiming to delineate current transfusion practices and, importantly, determine whether baseline demographic, clinical, cytogenetic, and molecular disease features were significantly correlated with transfusion intensity, overall response, achievement of remission, significant bleeding, and induction-related mortality. Our findings suggest a tight association between blood group type, increased use of FFP, and RBC transfusion requirements and overall survival in AML patients receiving intensive induction chemotherapy.

Transfusion dependency at initial diagnosis and during induction chemotherapy has been previously shown to be an independent determinant of patient prognosis in this clinical setting. Indeed, Cannas and colleagues from Lyon University Hospital showed in a historic cohort of AML patients treated over 2 decades until the mid-2000s that both response rate and overall survival were significantly impacted by increasing transfusion needs of both RBC and platelets [13]. Our data, in a recently treated patient cohort, extend on these findings by showing that a higher RBC as well as platelet transfusion burden during the induction phase was tightly associated with a lower initial hemoglobin level, a lower platelet count, increased initial LDH, and uric acid serum levels concomitant to increased use of platelet transfusions. Furthermore, the independent prognostic impact of an increased RBC transfusion load on patient survival was confirmed in multivariate analysis. Aiming to further delineate the differential impact of the various blood product components, we focused our analysis also on single donor platelets, showing that increased SDP transfusions intensity was tightly associated with admissions to the ICU during induction. Additionally, use of SDP infusions varied significantly according to patient blood group to the extent that blood group B patients were more likely to receive more
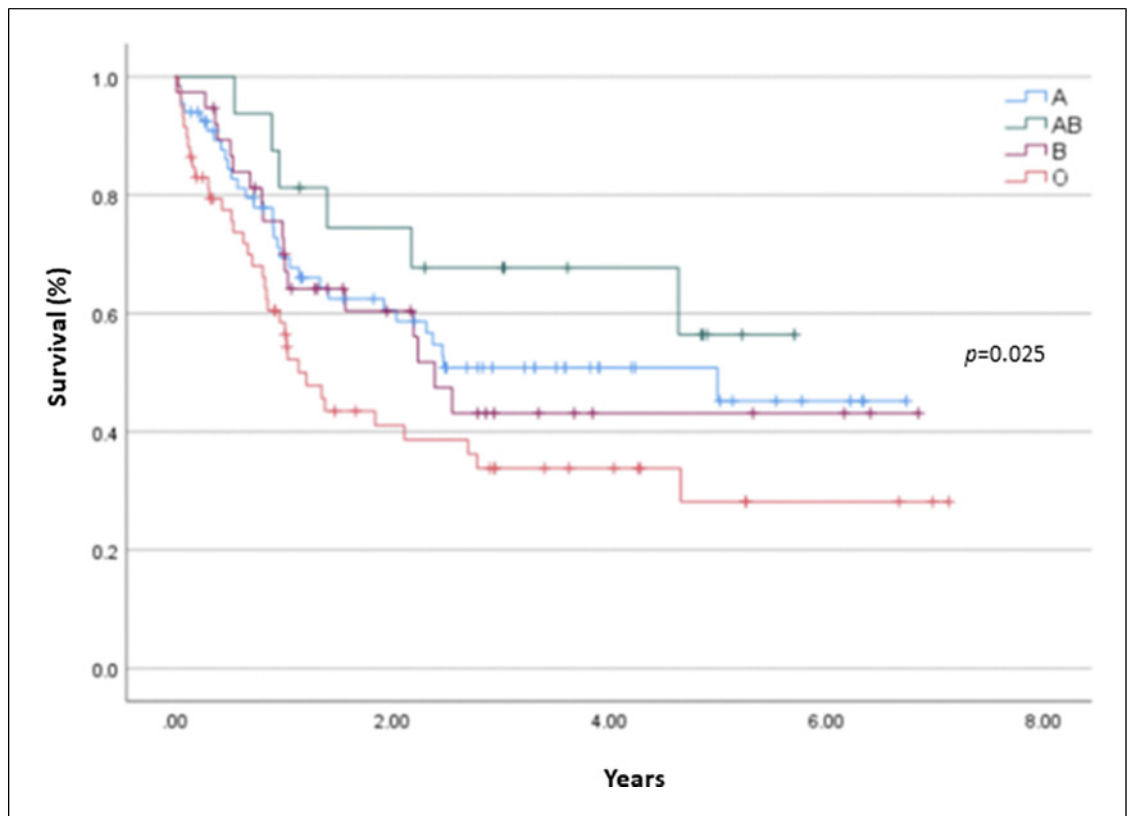
Miller/Freed-Freundlich/Shimoni/Hellou/
Avigdor/Misgav/Canaani

Fig. 1. Impact of blood group on overall survival of AML patients undergoing intensive induction chemotherapy.

than three SDP units during induction compared with patients with other blood groups. An additional unexpected finding our analysis generated was the observation that overall survival was significantly associated with patients' blood group. In point of fact, AB blood group patients were found to experience the longest survival, while blood group O patients had inferior survival compared to the patients with other blood groups. Indeed, the ABO blood group has been reported previously to be associated with risk and patient outcome in several solid malignancies such as colon cancer [28], esophageal cancer [29], pancreatic cancer [30]. Furthermore, in lymphoma patients, for example, a recent study revealed that patients with blood group B treated for diffuse large B-cell lymphoma experienced inferior 5-year survival compared to non-B group patients [31]. The reasons for these findings and the results of our current study are yet to be determined; however, an accruing body of evidence suggests that single nucleotide polymorphisms in the ABO gene, inflammation, alterations in red blood surface glycoconjugates, serum levels of P-selection, and soluble E-selectin may play a role in the neoplastic process and response to therapy [32–34]. Finally, it is noteworthy

that similar observations regarding the survival advantage of blood group AB patients have been previously made also in the non-oncology setting of patients admitted to the ICU [35] as well as patients recovering from cardiac surgery [36].

While use of FFP is uncommon in the setting of AML, as shown in a recent Australian random-sample survey [11], our study uncovered several noteworthy associations between the use of FFP and disease features, namely a higher FFP transfusion burden during induction was tightly associated with an increased WBC count at diagnosis which has been shown previously to correlate with lower survival rates in AML patients [37, 38]. Furthermore, compared with $FLT3^{wt}$ patients, $FLT3$-ITD-mutated patients were significantly more likely to receive an increased number of FFP units, an association which has not previously been reported in this patient population, further reflecting the aggressive nature of $FLT3$-ITD AML [39]. Indeed, receipt of FFP during induction was significantly associated with adverse patient outcome, resulting in a significantly lower likelihood of achieving remission, a significantly increased rate of induction-related mortality, higher admission rates to the
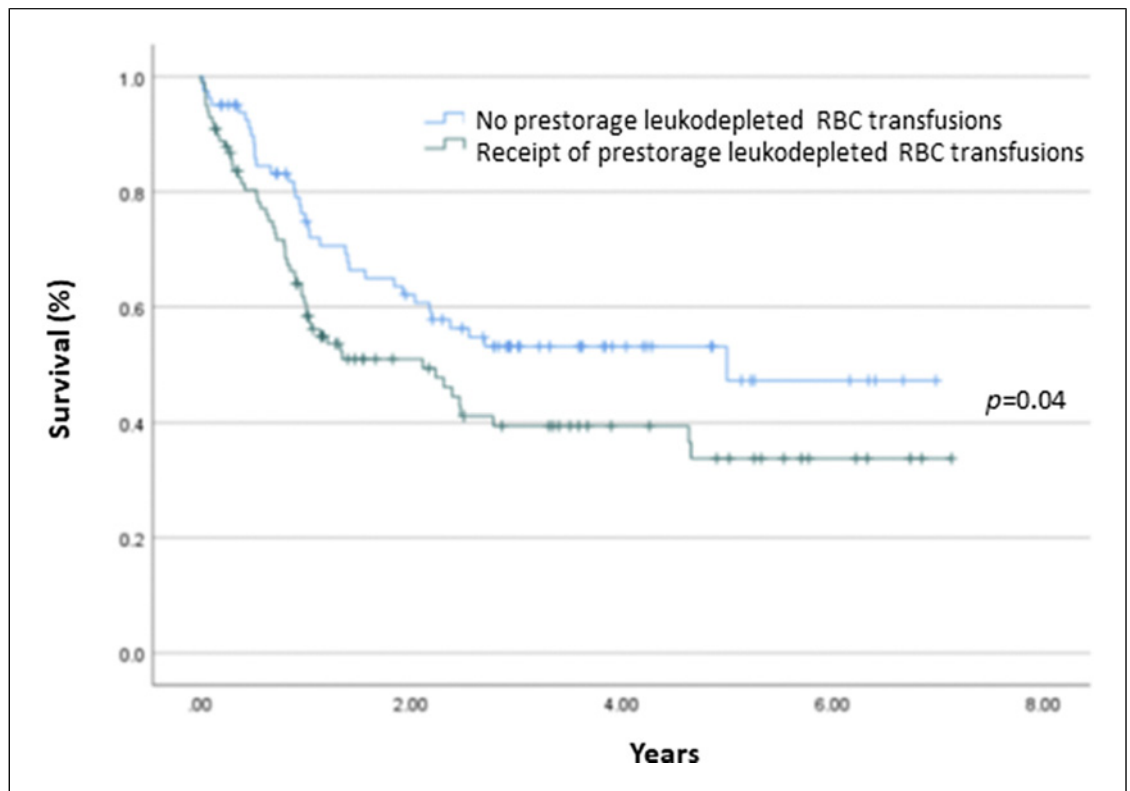
Fig. 2. Association of receipt of pre-storage leukodepleted RBC and overall survival in AML patients during induction chemotherapy.

medical intensive care unit, and worse overall survival confirmed in multivariate analysis. In concurrence with the aforementioned observations pertaining to FFP transfusions, we found that patients receiving cryoprecipitate during induction therapy experienced significantly higher induction-related mortality rates. Moreover, this patient subset was significantly enriched for the *FLT3-ITD* mutations. It is important to note that directives regarding the recommended use of cryoprecipitate in AML patients are not substantiated on randomized controlled studies and have been extrapolated from clinical data established in the setting of trauma [40] and surgery [41]. In the same vein, a survey conducted by Pine and colleagues, revealed that a fibrinogen threshold of 100 mg/dL was commonly used by leukemia physicians as the critical value triggering the receipt of cryoprecipitate, mostly in the setting of disseminated intravascular coagulation [16].

Our analysis revealed that 4% of the study cohort developed transfusion-associated alloimmunization which is in line with previous estimates for the general population of patients receiving RBC transfusions, indicating that 2%–5%

of patients develop detectable RBC alloantibodies [42, 43]. Our findings concur with the results of a previously published Austrian study of 184 patients with AML or myelodysplastic syndromes treated with azacitidine showing that the risk of alloimmunization was tightly associated with a higher number of transfused RBC units [44] and also with those of a cohort study from the Netherlands showing that the incidence of alloimmunization incidences increased to 7.7% in patients receiving more than after 40 RBC units [45].

Owing to the retrospective nature of this analysis, several limitations to interpretation of these data need to be recognized. The ELN 2017 risk stratification model used for assessing the patients in this study also encompasses evaluation of *ASXL1* and *RUNX1* which were not captured by the routine molecular panel used by our institution at the time of initial diagnosis. However, we note that a recent SWOG analysis showed that these mutations provide a limited overall contribution to risk stratification across the entire population, given the low frequency of mutations and confounding risk factors [46]. In addition, blood product management of the
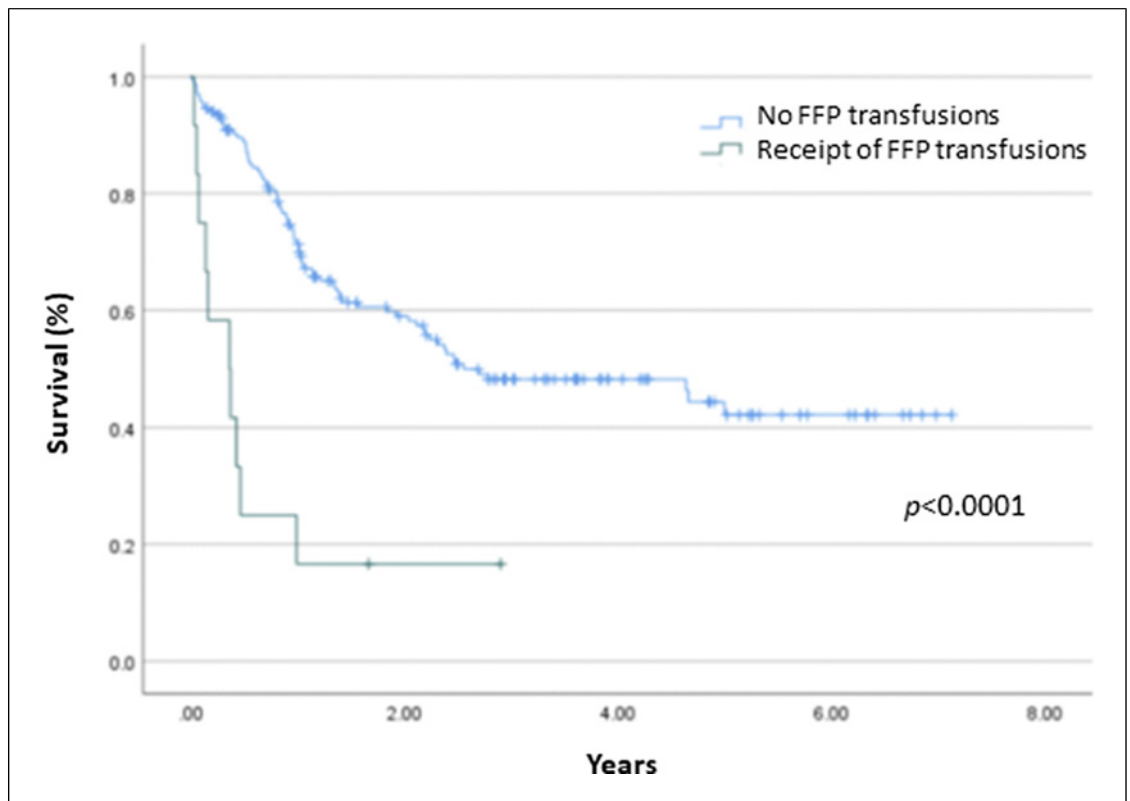
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Avigdor/Misgav/Canaani

Fig. 3. Assessment of the impact of FFP transfusions on patient survival during induction chemotherapy.

treated patients was based on the treating physician's choice; thus, the possibility of this being a confounding factor cannot be completely ruled out. An additional facet to consider in this setting is that administration of pre-storage leukodepleted versus bedside leukodepleted RBC transfusions impacted on patient outcome or the possible prognostic benefit of giving patients SDP infusions versus pooled donor platelets. However, as patients in this analysis were given both pre-storage leukodepleted and bedside leukodepleted RBC transfusions as well as both patients' SDP infusions and pooled donor platelets, depending on product availability at our institutional blood bank, analysis of the prognostic impact of specific blood products is not possible. Lastly, it is important to emphasize that while our data suggest a tight association between transfusion intensity and clinical outcome in AML patients receiving intensive induction chemotherapy, it is likely that in most instances, the severity of the leukemia dictates much of the clinical outcome with blood product support holding most likely an indirect role in determining clinical outcomes. Indeed, as discussed previously by Middelburg and colleagues, clinical

transfusion investigations necessitate cautious interpretation of data owing to the inherent possible biases (e.g., sicker patients receiving more transfusions resulting in poor outcome which relates more to the underlying disease rather than increased transfusion burden) [47].

At the provider level, it is essential that we identify specific patient subsets more likely to incur a higher transfusion burden as well as treatment and disease-related complications during intensive induction chemotherapy for newly diagnosed AML. Anticipating the transfusion needs of a given patient during the intensive induction phase will undoubtedly aid in resource allocation and planning. In this analysis, we comprehensively mapped the transfusion trajectory of AML patients during induction therapy and identified clinically meaningful associations impacting the need for the various blood components as well as overall survival. As less intensive induction approaches such as combination therapy based on *bcl-2* inhibition with venetoclax gain traction, it will become increasingly important to determine the clinical trajectory of these patients in terms of blood product utilization.

Statement of Ethics

All research complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This is a retrospective analysis of data, no participants were recruited. Written informed consent from participants was not required in accordance with local/national guidelines. This retrospective data analysis was approved by the Institutional Review Board.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Jonathan Canaani and Liron Miller designed the research and/or analyzed the data. Jonathan Canaani wrote the manuscript. Mor Freed-Freundlich, Tamer Hellou, Avichai Shimoni, Abraham Avigdor, and Mudi Misgav provided clinical data and commented on the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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