Blood Product Requirement in Childhood Acute Myeloid Leukemia by Chemotherapy Regimens

Çocukluk Çağı Akut Myeloid Lösemilerde Kan Ürünü Kullanımının Kemoterapi Bloklarına Göre Dağılımı

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ABSTRACT

Objective: This study evaluates total erythrocyte, random platelet and apheresis platelet suspension requirement in pediatric acute myeloid leukemia (AML) patients in relation to ongoing chemotherapy (CT) regimens.

Material and Methods: A total of 37 pediatric patients diagnosed with AML were included in this retrospective study. Data on patient demographics (age, gender), age at diagnosis, type of CT protocol, completion of CT protocol and amount of blood product use (erythrocytes, apheresis platelet and random platelet) and survival during CT were retrieved from hospital records.

Results: The total number of erythrocytes, apheresis platelets and random platelets received by 37 AML patients from the date of diagnosis were 1275 (mean (min-max): 27 (10-102) bags), 1287(mean (min-max): 25 (-99 bags) and 1237(mean (min-max): 20 (7-139) bags), respectively.

AIE as followed by maintenance treatment was associated with the highest amount of erthryocyte ($p<0.001$) and apheresis platelet ($p<0.001$) use when compared to other CT regimens, while maintenance treatment as followed by AIE was associated with the highest amount of random platelet use ($p=0.008$) as compared with other CT regimens. No significant difference was noted between AI and haM protocols in terms of blood product use, while apheresis platelet and random platelet use were lowest with HAM treatment ($p<0.001$ and $p=0.008$, respectively).

Conclusion: In conclusion, our findings indicate a great amount blood product transfusion to be required in children with AML under chemotherapy and emphasize the likelihood of transfusion need to alter with respect to ongoing CT regimen.

Key Words: Acute myeloid leukemia, Blood products, Chemotherapy, Child, Transfusion

ÖZ

Amaç: Bu çalışmada; akut myeloid lösemi (AML) tanılı çocuk hastalarda toplam eritrosit, random trombosit ve aferez trombosit süspansiyonu gereksiniminin, hastanın o dönemde almış olduğu kemoterapi (KT) bloğu ile olan ilişkisi değerlendirildi.

Gereç ve Yöntemler: Bu retrospektif çalışma, toplam 37 pediatrik AML hastasında yürütülmüştür. Hastaların demorgrafik özellikler, KT protokolü ve kan ürünleri gereksinimi (eritrosit, aferez ve random trombosit) ve sağkalıma dair veriler hastane kayıtlarından elde edildi.

Bulgular: Tanıdan itibaren toplam eritrosit, aferez trombosit ve random trombosit kullanım miktarları sırasıyla, 1275 (ortanca (min-maks): 27 (10-102) adet), 1287(ortanca (min-maks): 25 (6-99 adet) ve 1237(ortanca (min-maks): 20 (7-139) adet) olarak bulundu. AIE ve onu izleyen idame blokları, diğer KT bloklarına göre en yüksek eritrosit ($p<0.001$) ve

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Contribution of the Authors / *Yazarların katkısı* : *GUDELOGLU E:* Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ALBAYRAK D:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***ALBAYRAK C:*** Constructing the hypothesis or idea of research and/or article, Reviewing the article before submission scientifically besides spelling and grammar.

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aferez trombosit (p<0.001) kullanım miktarı ile ilişkili bulunurken, idame ve onu izleyen AIE en yüksek random trombosit kullanım miktarı ile ilişkiliydi (p=0.008). AI ve haM protokolleri arasında kan ürünü kullanım miktarı açısından anlamlı bir fark gözlenmezken, HAM protokolü en düşük aferez trombosit ve random trombosit kullanım miktarları ile ilişkili bulundu (sırasıyla, p<0.001 ve p=0.008).

Sonuç: Sonuç olarak bulgularımız, AML tanılı çocuk hastalarda büyük miktarda kan ürünü transfüzyon gereksinimine ve bu devam eden KT rejiminin bu gereksinim üzerindeki olası değiştirici etkisine işaret etmektedir.

Anahtar Sözcükler: Akut myeloid lösemi, Kan, Kemoterapi, Çocuk,Transfüzyon

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous malignant disease group characterized by the uncontrolled proliferation of progenitor cells of the myeloid series in the bone marrow. Although it is more common in adults, it constitutes 15-25% of childhood acute leukemia and considered to be responsible for 30% of deaths due to childhood leukemia (1-3).

Although the survival rate for pediatric AML continues to rise due to modern oncological therapies (1). AML is a disease which requires frequent transfusion of erythrocyte and platelet suspensions during treatment in relation to treatment-related severe and sustained cytopenias.

To our knowledge no study to date has investigated the blood product requirement pediatric AML patients with respect to type of ongoing chemotherapy regimen.

The aim of this study is therefore to evaluate for the first time in the literature, association of total erythrocyte, random platelet and apheresis platelet suspension requirements in pediatric AML patients under chemotherapy (CT) and to assess the relation of different CT regiments with the blood product requirement.

MATERIAL and METHOD

A total of 51 patients diagnosed with AML were enrolled in this retrospective study conducted at Pediatric Hematology clinics between January 2005 and January 2014. Of 51 patients initially enrolled, 37 patients were subjected to the final analysis after exclusion of 14 patients due to follow up at another hospital (n=7) and missing data on blood bank or hospital information management system (n=7). The relapse periods of patients who were followed with a diagnosis of AML but were relapsed were excluded.

Data on patient demographics (age, gender), age at diagnosis, type of CT protocol (AIE followed either by “AI, haM” or “ HAM, AI, hAM” and then by HAE and maintenance), completion of CT protocol and amount of blood product use (erythrocytes, apheresis platelet and random platelet) and survival during CT were retrieved from hospital records.

AML BFM 98 and AML BFM 2004 treatment protocols are applied in our clinic in routine management of AML patients. Standard risk group AML patient treatment schedule starts with AIE Protocol and ends with AI, haM and HAE and maintenance. High risk group AML patient treatment schedule; starts with AIE Protocol and ends with HAM, AI, hAM, HAE and maintenance.

The total number of erythrocyte, random platelet and apheresis platelet suspension requirements of each AML patient from the date of diagnosis to the end of the treatment were retrived from blood bank records. The use of blood products between CT protocols were recoded based on total number of blood cells and bags.

In our department, erythrocyte transfusion indication in children with AML includes administration of 15 ml/kg (500 ml at most) erythrocyte suspension (ES) when blood hemoglobin concentration is lower than 8 g/d or hematocrit level is lower than 24% (4-8). The dose of ES is 15 ml/kg for ≤20 kg patients, and 500 ml (two units) at most for patients > 20 kg. In the blood bank of our hospital, ES with an average volume of 250 ml per unit (one bag=one=one unit) prepared with Saline +Adenine +Glucose+Mannitol (SAG-M) with 55-60 % hematocrit is used and it can be kept up to 42 days at 1° – 6° C in the refrigerator. However, the erythrocyte used in patients with acute leukemia are 5-7 day erythrocytes in the form of ES irradiated at 2500 cGy dose and they undergo inline leukocyte filter application before being stored in the blood bank (2-6).

Platelets are kept at 20-24 C° in the blood bank of our hospital and due to risk for bacterial infection at this temperature; the period of keeping platelet is limited to only five days. At the end of five days, platelets lose their vitality by 20-25% (2-6). In our hospital, there are two types of platelet suspension (PS) as apheresis and random with a unit (one bag=one=one unit) volume of 60 ml on average. Our first choice in patients with thrombocytopenia is administration of apheresis platelet, given that it includes more intense platelet in a smaller volume (a unit of apheresis platelet suspension corresponds to 6-8 random-donor (random) platelet suspension in terms of the number of platelets). If apheresis platelet cannot be obtained, random platelet suspension calculated as one unit to 10 kg is given (2-6). In our hospital, the criteria for platelet suspension treatment in children with AML is platelet levels of < 30.000/ µl under normal conditions and platelet levels of < 40.000 / µL in the course of infection. The study protocol was approved by the OMU Ethic Committee (KAEK 2014/748).

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). Normality

assumption was tested with Kolmogorov Smirnov test. Kruskall Wallis with Bonferroni correction and Mann Whitney U test were used in the analysis of continuous data. Data were expressed as "mean (minimum-maximum) and percent (%) where appropriate. p<0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics and survivorship status

Overall, females composed 40.5% of the study population and 65.0% of patients were in the 1-9 years age group. AIE and AI were applied in all patients, along with haM (92.0%), HAE (79.0%), HAM (65.0%) or maintenance (70.0%) protocols (Table I).

In total 7 (18.9%) patients did not survive to treatment completion including 5 male and 2 males. The last regiment before death was HAM (n=2), haM (n=3) or maintenance (n=2) among non-survivors (Table I).

Table I: Demographic and clinical characteristics and survivorship status.

	n(%)
Age*	
≤ 1 and ≥9	13(35.0)
1-9	24(65.0)
Gender*	
Male	22(59.5)
Female	15(40.5)
CT protocol*	
AIE	37(100.0)
AI	37(100.0)
haM	34(92.0)
HAE	29(79.0)
HAM	24(65.0)
Maintenance	26(70.0)
Survivorship status*	
Survivor	30(81.1)
Non-survivor	7(18.9)
Male	2
Female	5
Last CT regimen	
HAM	2
haM	3
Maintenance	2

*:*n(%)*

Blood product use according to CT regimens

The total number of erythrocytes, apheresis platelets and random platelets received by 37 AML patients from the date of diagnosis were 1275 (mean (min-max): 27 (10-102) bags), 1287(median (min-max): 25 (6-99 bags) and 1237(median (min-max): 20 (7-139) bags), respectively. In those who completed the all steps of CT protocols (n=25), the total number of erythrocytes, apheresis platelets and random platelets were 828 (median (min-max): 24 (10-102) bags), 738 (median (min-max): 23 (6-88 bags) and 853 (median (min-max): 19 (7-139) bags), respectively (Table II).

The AIE block as followed by maintenance treatment was associated with the highest amount of erthryocyte (p<0.001) and apheresis platelet (p<0.001) use when compared to other CT regimens, while maintenance treatment as followed by AIE was associated with the highest amount of random platelet use (p=0.008) as compared with other CT regimens (Table II). No significant difference was noted between AI and haM protocols in terms of blood product use, while apheresis platelet and random platelet use were lowest with HAM treatment (p<0.001 and p=0.008, respectively) (Table II).

DISCUSSION

Demographic characteristics of patients in our cohort seems consistent with male predilection and age at onset (range, 8.2 to 11.5 years) of the childhood AML reported in past studies (9-17).

Table II: Blood product use according to CT regimens.

	Erythrocyte			Apheresis platelet			Random platelet		
	n	Total number	Median per patient (min-max)	n	Total number	Median per patient (min-max)	n	Total number	Median per patient (min-max)
Total	37	1275	27 (10-102)	37	1287	25 (6-99)	37	1237	20 (7-139)
Completed treatment	25	828	24 (14-102)	25	738	23 (6-88)	24	853	19 (7-139)
CT regimen									
AIE	37	330	8 (2-20)^{B}	36	352	9 (1-28)^{A}	29	357	11 (2-31)^{A}
HAM	23	97	3 (1-10)^{A}	21	61	3 (1-10)^{B}	14	71	5 (3-9)^{B}
AI	35	214	4 (1-39)^{A}	29	205	4 (1-49)^{AB}	19	130	5 (2-16)^{AB}
haM	33	181	5 (1-16)^{A}	28	168	5 (1-25)^{AB}	14	123	5 (2-34)^{AB}
hAE	27	200	6 (1-49)^{AB}	27	223	4 (1-74)^{AB}	16	188	9 (1-46)^{AB}
Maintenance	15	253	7 (1-57)^{AB}	13	278	7 (2-66)^{A}	11	369	27 (1-102)^{AB}
p value			**0.001**			**<0.001**			**0.008**

A, B, AB: *No differences between blocks with the same letter for each, CT protocol in terms of blood product use*

In general AML is associated with an acute onset and heterogeneous nature of admission symptoms depending on the degree of bone marrow deficiency or the width of extramedullar expansion (9). Nonetheless, a need for frequent blood and blood product transmission is commonly encountered during treatment of AML patients, given the high prevalence of hemorrhage symptoms (13).

Supportedly, our findings indicate the high need for blood products during chemotherapy of AML patients with average 27, 25 and 20 bags of erythrocytes, apheresis platelets and random platelets received during the treatment course. This seems notable given the consideration of blood transfusion requirement to be one of the most significant cost driver associated with the management of AML (18). Our findings revealed association AIE and maintenance regimens with highest amount of erthryocyte, apheresis platelet and random platelet use, whereas lower need for apheresis platelet and random platelet transfusion under HAM treatment in AML patients.

No study to date has addressed the amount of blood product use in pediatric AML patients under chemotherapy. In a past study among eldery AML patients, authors noted the association of low-intensity treatments with requirement of a reduced number of transfused blood products as compared with intensive chemotherapy, and indicated low intensity treatment to be a cost-effective alternative to best supportive care (18). Notably, the AZA-001 study showed that, compared with conventional care regimes (CCR), myelodysplastic syndrome (MDS) patients receiving AZA had prolonged median survival, had delayed progression to AML, had reduced dependence on transfusions (19). Significant difference in the amount of blood product use according to CT protocol in our cohort pediatric AML patients seems notable in this regard.

Transfusion of blood products is a key component of the supportive management in patients with acute leukemia (20). Indeed, in a past study among AML patients belonging to the denomination of Jehovah's Witnesses (JW), who are bound by their religious convictions not to accept blood products, reduced dose chemotherapy without transfusion support was reported to be associated with a lower rate of remission, high mortality by severe anemia and very low chances for long-term remissions (21). However, due to lack of standardized evidence-based guidelines for blood product transfusions, a wide variation exist in blood product transfusion practices across several clinical scenarios. Hence a need for developing specific transfusion goals for blood products for acute leukemia patients is emphasized for limiting unnecessary transfusions without compromising outcomes (20).

The current study, providing data for the first time in the literature on blood product use in relation to chemotherapy protocols among pediatric AML patients, emphasize frequent transfusion need in AML patients and informs both families and blood bank authorities about how much the need for transfusion can increase numerically in some steps of the treatment.

In conclusion, our findings indicate a great amount blood product transfusion to be required in children with AML under chemotherapy and emphasize the likelihood of transfusion need to alter with respect to ongoing CT regimen. The efficiency of the transfusion can depend on many factors such as the type of acute leukemia, patient age, patient gender, CT regimen, or concomitant infection, sepsis, or intense consumption coagulopathy. Our findings emphasize need for large prospective randomized trials to address requirement of blood products in AML populations with respect to patient profile, concomitant disorders and treatments, to improve blood product transfusion practice in AML patients and to prevent unnecessary transfusions.

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