A STUDY ON EFFECTIVENESS OF LEUKEPHERESIS IN PATIENTS WITH HYPERLEUKOCYTIC LEUKEMIAS

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ABSTRACT

Background: Thrombosis is a common complication of hyperleukocytic leukemias. **Purpose:** To access features of leukostasis, effectiveness of leukopheresis in terms of reduction of WBC, and biochemistry indicators in hyperleukocytic leukemias. ***Patients and methods:*** An intervention study was carried out on 112 CML patients treated with leukopheresis in Hai Phong Vietnam - Czech friendship hospital from 7/2017 to 3/2019. ***Results:*** (1) Clinical symptoms of leukostatsis: (a) Percentage of symptoms: headache/dizziness: 38,0%; visual impairment/hearing loss: 2,0%; splenic pain/infarct: 12,0%; priapism: 2,0%; leukostasis related pulmonary distress syndrome: 2,0%; CNS hemorrhage: 2,0%. (2) Effectiveness of leukopheresis in term of reduction of WBC, and biochemistry indicators in hyperleukocytic leukemias: (a) WBC reduced significantly after leukopheresis and after 24 hours: CML: 304, 219 and 198 G/l; AML: 295, 206 and 194 G/l; ALL: 342, 207 and 185 G/l, respectively (with P<0,01); (b) Cytoreduction effectiveness after leukopheresis in CML, AML and ALL after 24 hours are: 34,7%; 34,2% and 45,9% respectively. (3) Change of blood uric acid and LDH concentrations after leukopheresis: (a) Uric acid concentration reduced significantly for males and females after leukopheresis; (b) LDH concentration reduced significantly (CML: 3.129 and 1.892 U/l; AML: 2.589 and 1.491 U/l; ALL: 2.992 and 1712 U/l (P<0,01) before and after leukopheresis, respectively (with P<0,01). **Conclusion:** Leukopheresis is an effective supportive treatment for hyperleukocytic leukamias.

Keywords: *Acute myeloid leukemia (AML), Acute lympho leukemia (ALL), chronic myeloid leukemia (CML), leukopheresis, hyperleukocytic symptoms, Clinical symptoms of leukostatsis.*

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I. INTRODUCTION

An increased number of white blood cells (WBC) (more than 100G/L) in peripheral blood is a common manifestation leukemia. For CML, the proportion of patients with high WBC count accounts for 70-90%. For ALL, this rate is about 10-21%. An increase in the number of WBC leads to leukemia, which causes complications of thrombosis, hemorrhage and the risk of tumor lysis syndrome [1],[4].

Leukopheresis is an effective way of treatment of hyperleukocytic leukemias, which helps to prevent and treat above complications. [1],[2],[6]

Automated cell separation has been used frequently at Center of Hematology- Blood Transfusion, Hai Phong Vietnam-Czech hospital to treat patients with hyperleukocytic leukemias. In order to evaluate the effectiveness of this method, we conduct the study: "Effectiveness of Leukopheresis in

patients with hyperleukocytic leukemias" with purposes:

1. Clinical features of patients with hyperleukocytic leukemias

2. Change in WBC count and some related biochemical indicators after leukopheresis

II. SUBJECT AND METHOD

2.1. Subject of the study

- There were 112 patients with hyperleukocytic leukemias, in which 84 CML patients, 16 AML patients, 12 ALL patients

- Study time: From 7/2017 to 7/2019.

- Research site: Hematology department, Hai Phong Vietnam - Czech friendship hospital

2.2. Research method

2.2.1. Research design

- Cross-sectional study, progressive, clinical intervention (Leukopheresis)

2.2.2. Patient selection criteria

- Patients who were diagnosed ALL, AML, CML with WBC above 100 G/L.

- Indication for leukopheresis: WBC count above 100 G/L, minimum PLT count above 30 G/l.

Perform leukopheresis using Trima - Obtia machine based on the standard of the National Institute for Hematology - Blood Transfusion. Then the patients were treated with chemotherapy (hydroxyurea or multiple chemotherapy).

2.2.3. Research indices

- Clinical examination reveals symptoms of leukocytosis and circulatory stasis: headache, dizziness, decreased or loss of vision or hearing, shortness of breath, focal neurological signs, paralysis or comatose.

- Peripheral WBC: done at different times: right before, right after, after 12h and after 24h of leukopheresis

- Blood indices: acid uric, LDH concentration: done at right before and 24h after leukopheresis

2.2.4. Data analysis

- The data was analyzed using SPSS 15.0.

2.2.5. Ethical issue

- The study was done based on the regulations in ethical issue. The research result was used only for research and patients, all the information relating to patients were kept confidential.

III. RESULTS:

3.1. Common features of patients

In our research, average age of patients was 38 ± 21. The oldest was 61, lowest was 19. There were 67 male patients (59,8%) and 45 female patients (40,2%). Number of CML was 84 (75%). The number of AML patients was 16 (14,3%). Number of ALL patients was 12 (10,7%).

3.2 Clinical manifestations of hyperleukocytic leukemias and circulatory stasis

The following tables and graphs describe the features and percentage of clinical manifestations.

Table 1. Percentage of leukostasis in patients with hyperleukocytic leukemias

Clinical manifestations (n and %) WBC count		Headache, dizziness numbness	Decreased vision or hearing	Spleen pain	Penile veous thrombosys	Lung leukemia	Stroke
WBC 100-200 G/l (n=15) (level 1)	(1)	2 (13,3%)	0 (0%)	1 (6,7%)	0 (0%)	0 (0%)	0 (0%)

Clinical manifestations (n and %) / WBC count		Headache, dizziness numbness	Decreased vision or hearing	Spleen pain	Penile veous thrombosys	Lung leukemia	Stroke
WBC above 200-300 G/l (n=47) (level 2)	(2)	10 (21,3%)	1 (2,1%)	5 (10,6%)	1 (2,1%)	0 (0%)	1 (2,1%)
WBC above 300 G/l (n=50) (level 3)	(3)	19 (38,0%)	1 (2,0%)	6 (12,0%)	1 (2,0%)	1 (2,0%)	1 (2,0%)
P_{1-2}		<0,05	<0,05	<0,05	>0,05	>0,05	>0,05
P_{2-3}		<0,05	>0,05	>0,05	>0,05	>0,05	>0,05
P_{1-3}		<0,05	<0,05	<0,05	>0,05	>0,05	<0,05

Among 112 patients of 3 groups, percentage of leukostasis as below:

Graph 1. Clinical manifestations of leukostasis (%)
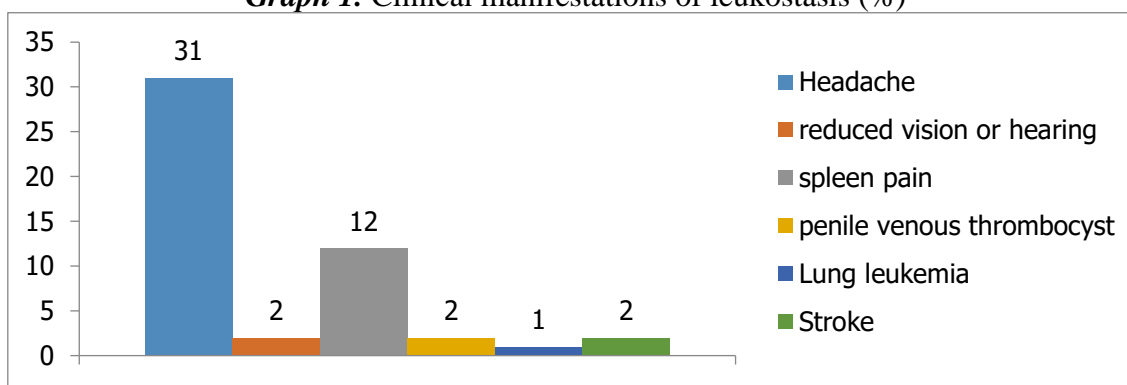
3.3. Change in WBC count and some blood indices after leukopheresis

3.3.1. Change in WBC count

The following tables and graphs describe WBC count at the time before, right after, after 12 hours and after 24 hours.

Table 2. Change in peripheral WBC count after leukopheresis

WBC (G/l) (X±SD) / Group	Before (1)	Right after (2)	After 12h (3)	After 24h (4)	P_{1-2}	P_{2-3}	P_{3-4}	P_{1-4}
CML (n=84)	304 ± 156	219 ± 147	210 ± 136	198 ± 122	<0,01	>0,05	<0,01	<0,01
AML (n=16)	295 ± 131	206 ± 135	202 ± 109	194 ± 135	<0,01	>0.05	<0,01	<0,01
ALL (n=12)	342 ± 126	207 ± 114	198 ± 116	185 ± 122	<0,01	>0.05	<0,01	<0,01

The reduce in number of WBC in 3 groups of patients with CML, AML and ALL after 24 hours is 34,7%; 34,2%, 45,9%, respectively. The details are presented in graph 2.

Graph 2. Efficiency of leukocytosis after leukopheresis according to disease
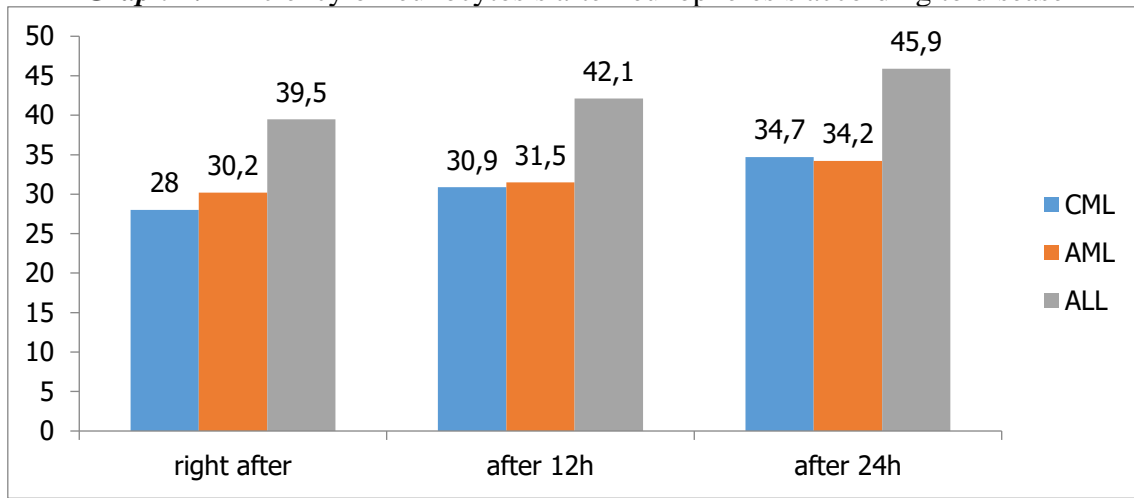

Table 3. Change in peripheral WBC count after leukopheresis according to WBC level

WBC (G/l) (X±SD) / WBC count	Before (1)	Right after (2)	After 12h (3)	After 24h (4)	P_{1-2}	P_{2-3}	P_{3-4}	P_{1-4}
WBC 100-200 G/l (n=15) level 1)	168± 101	113± 96	109± 95	102± 93	**<0,01**	>0,05	**<0,01**	**<0,01**
WBC above 200-300 G/l (n=47) (level 2)	265 ± 123	199± 112	193± 99	184 ± 95	**<0,01**	>0,05	**<0,01**	**<0,01**
WBC above 300 G/l (n=50) (level 3)	382 ± 135	302± 126	290± 121	284± 109	**<0,01**	>0,05	**<0,01**	**<0,01**

Based on efficiency of WBC reduction, there are differences in 3 levels of WBC level (level 1:100-200G/l), (level 2: above 200-300 G/l), (level 3: above 300 G/l) before and after leukopheresis. The details are presented in the following graph

Graph 3. Change in WBC count after leukopheresis of each WBC level
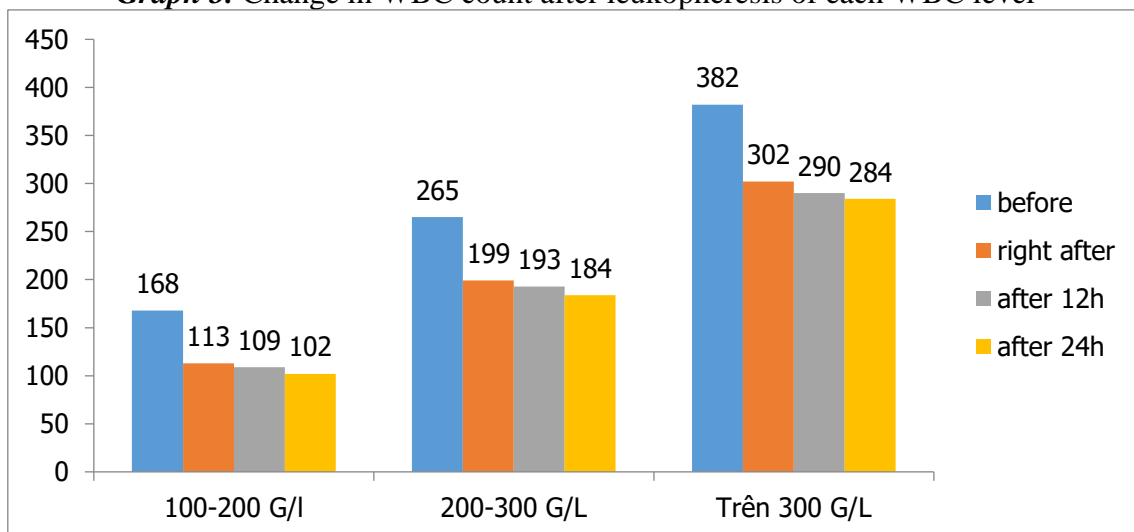
3.3.2. Changes in some related blood indices after leukopheresis

The following tables and graphs describe the changes in acid uric and LDH concentration at the time of before and after 24 hours.

Table 4. Acid uric concentration before and after leukopheresis

Acid uric (µmol/l) (X ± SD) WBC count	Male			Female		
	before	After 24h	P	Before	After 24h	P
CML (n=84)	396±245	325±187	<0,01	279±198	221±132	<0,01
AML (n=16)	382±221	316±165	<0,01	293±125	243±126	<0,01
ALL (n=12)	389±178	309±154	<0,01	289±98	217 ± 103	<0,01

Table 5. LDH concentration before and after leukopheresis

LDH (U/l) (X±SD) Type	Before	After 24h	P
CML (n=84)	3.129 ± 2.612	1.892 ± 1.232	<0.01
AML (n=16)	2.589 ± 1.925	1.491 ± 1.357	<0.01
ALL (n=12)	2.992 ± 1.556	1.712 ± 1.121	<0.01

IV. DISCUSSION

4.1. Clinical manifestations of leukocytosis and circulatory stasis

In our research, the most common symptoms are headache/ dizziness, numbness. Although some cases can be related to anemia, the increased rate of these symptoms has statistical significance (P<0,05) (depending on the WBC level (level 1:100-200G/l), (level 2: above: 200-300 G/l), (level 3: above 300 G/l)), which shows that the main mechanism is leukostasis as a result of the leukocytosis syndrome.

For more severe complications due to leukostasis such as vision/hearing loss and spleen pain/ splenic infarction, the number of patients have clinical symptoms is relatively low. However, we still find the relevance between clinical manifestations and leukocytosis level. Specifically, there was a significant difference (P <0.05) between level 1 and level 3 for symptoms of more severe leukocytosis such as visual / hearing loss and splenic pain /spleen infarction.

In particular, severe manifestations of leukocytosis such as lung damage and stroke, although seen in a very small proportion of patients, are in the group with a very high increase in WBC: 1 patient at level 2, especially 1 patient at level 3 (above 300 G/l).

4.2. Change in WBC count and blood indices after leukopheresis

4.2.1 Change in peripheral WBC count

The study shows a significant reduction in WBC count right after leokopheresis in all 3 groups CML, AML and ALL with P<0,01. WBC count continued to reduce in 24 hours and down to: 198 ± 122; 194 ± 135 and 185 ± 122 G/l, respectively in 3 groups (P<0,01). Our research result is relevant to other results of De Santis, Porcu and Novotny [2,3,4]

Based on efficiency of leukocytosis, the reduction percentage of WBC count of 3 groups CML, AML, ALL was 34,7%; 34,2% and 45,9%, respectively. This result is consistent with the result of international researches [2],[6]. This efficiency tends to exceed the expectation of achieving effective cytoreduction (up to 30% WBC count) immediately after first leukopheresis [4].

The research also shows WBC count reduced significantly right after leukopheresis and especially after 24 hours at 3 levels of 100-200, above 200-300 and above 300 G/L, with the amount before and after 24h, respectively was: from 168 ± 101G/l to 102 ± 93 G/l; from 265 ± 123 G/l to 184 ± 95 G/l; and from 382 ± 135 G/l to 284 ± 109 G/l (P<0,01).

However, WBC count did not change much (P>0,05) at mediate time (after 12 hours) in compared with the time right after and after 24 hours. The reason we performed the test of counting peripheral blood cell index at many times was to choose the right time, allowing to measure the level of leukopenia accurately, reflecting the efficiency of leukopeheresis. Thus, it can be seen that the two appropriate times to evaluate the degree of leukopenia is immediately after and after 24 hours. The time after 12 hours does not reflect the significant change of WBC count after leukopheresis compared to the two times mentioned above.

4.2.2. Change in some related blood indices after leukopheresis

The result shows that acid uric concentration decreased significantly after leukopheresis at 3 groups CML, AML, ALL with P<0,01, at both male and female patients. This is an important evidence to reveal the effectiveness of leukopheresis in reduce the risk of tumor lysis syndrome [5,6].

Before leukopheresis, LDH average value increased in all 3 groups of CML, AML and ALL with 3.129 ± 2.612; 2.589 ± 1.925; 2.992 ± 1.556, respectively: after 24h of leukopheresis, LDH concentration reduced significantly at 3 groups with 1.892 ± 1.232; 1.491 ± 1.357 and 1.712 ± 1.121, respectively (p<0,01). Highly increased LDH is the signal of tumor lysis symdrome [5]. Therefore, leukopheresis is not only effective in reducing WBC and blood viscosity, preventing embolism, risk of tumor lysis syndrome, facilitating chemotherapy.

V. CONCLUSION

After studying on 112 patients with AML, ALL, CML with leukocytosis (above 100G/L) using leukopheresis, we draw out some conclusions:

5.1. Features of patients

- Percentage of clinical symptoms: headache/ dizziness/numbness: 31,0%. Vision/hearing loss: 2,0%. Spleen pain/ splenic infarction: 12%. Penile vein occlusion: 2%. Lung leukocytosis: 1,0%. Stroke: 2%.

5.2. Change in WBC count and some related blood indices

- WBC count decreased significantly at 3 groups, with the amount before leukepheresis and after 24 hours of leukepheresis respectively was: CML: 304, 219 and 198 G/l; AML: 295, 206 and 194 G/l; ALL: 342, 207 and 185 G/l.

- Efficiency of leukocytosis in 3 groups CML, AML and ALL after 24 hours was: 34,7%, 34,2% và 45,9%, respectively.

- Acid uric concentration decreased significantly in 3 groups, in both male and female.

- LDH concentration decreased significantly within 24 hours after leukopheresis in 3 groups, with the amount before and after respectively: CML: 3129 and 1.892 U/l; AML: 2589 and 1491 U/l; ALL: 2.992 and 1712 U/l.

VI. RECOMMENDATION

Leukopheresis is an effective and safe treatment. It is recommended for patients with ALL and CML with high WBC (above 100G/l) by using automated cell separation machine.

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