

DISORDERS OF HAEMOSTASIS, COMPLICATIONS AND THEIR CORRECTION IN CHILDREN WITH ACUTE LEUKEMIA

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Abstract

To study the significance of capillarotrophic disorders in the development of complications of chemotherapy in children with acute leukemia and the effectiveness of the treatment and prevention of these complications. Subjects and methods. Parameters of hemostasis system (plasma, platelet and vascular chains) have been studied in 86 children aged 1–17 years with acute leukemia in the follow-up of the condition, before the start and secondary to chemotherapy during the development of infectious and non-infectious complications. The patients receiving standard therapy in compliance with the BFM protocols were divided into two groups according to the difference in the substitution therapy: Group 1 included patients who did not receive platelet replacement therapy; Group 2 comprised patients who received replacement therapy, including preventive platelet transfusion. The effectiveness of therapy was accessed by comparing the number of complications in patients of both groups. Results. Severe myelosuppression was observed in 100% of patients. A decrease in the number of platelets in the blood lower than $20 \times 10^9/l$ was found in 43% of patients, agranulocytosis was found in 35%. Group 1 patients had bleeding in 33% of cases, stage II-III anemia in 76%, gastroenterologic inflammation in 21%, respiratory distress syndrome in 33%, pneumonia in 47%, sepsis in 14%, other localization of infection in 13%. In Group 2 patients the incidence of complications of chemotherapy and their severity decreased by 2–6 times. The concept of the leading role of thrombocytopenia in the development of stages of capillarotrophic disorders is presented. Conclusions. The results indicate the important role of severe thrombocytopenia and capillarotrophic disorders in the development of infectious and non-infectious complications of chemotherapy in patients with acute leukemia. Adequate replacement therapy with donor platelets reduces the incidence and severity of complications, increases the effectiveness of treatment.

Key words: *acute leukemia, children, complications, correction, hemostasis.*

Introduction

Disorders in the system of hemostasis in patients with acute leukemia occur due to underlying disease, but even more often they occur as a result of myelodepression as a complication of polychemotherapy (PCT). Hemorrhagic syndrome and neutropenia are severe complications of PCT, that worsen the course and prognosis of the disease [1–6]. Due to modern therapy of acute leukemia (AL) according to BFM protocols remission is achieved in 80–90% of patients [3, 7, 8]. However, the use of high-

dosage, multi-component, prolonged PCT is accompanied by numerous complications affecting prognosis of the disease [1, 7, 9, 10]. Improvement of supportive therapy, prediction and timely elimination of these complications allows to improve the final result of therapy [7, 8, 11].

2 Purposes, subjects and methods:

2.1 Purpose – study the parameters of the hemostasis system in children with acute leukemia at various stages of the disease, to determine the importance of thrombocytopenia in the development of capillarotrophic disorders and complications of PCT, and the role of transfusion of platelets as substitution therapy.

2.2 Subjects & Methods

The parameters of platelet, plasma, vascular components of the hemostasis system were studied in 86 children aged 2 to 18 years with

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acute leukemia (AL) using autocoagulation test (ACT) according to Z.S. Barkagan [12], prothrombin index, fibrinogen level, total protein in the blood serum, platelet count in peripheral blood, permeability of capillaries (PC) according to Kaznacheev [12]. The studies were carried out before the start of treatment and secondary to PCT with complications. An analysis of the complications of PCT and a comparison of their frequency and severity in two groups of AL patients of intensive care unit of Kharkiv Municipal Children Hospital No. 16 has been performed. Group 1 included patients (n = 42) with acute lymphoblastic leukemia (ALL), who underwent PCT and supportive therapy according to the protocol of treatment. Group 2 included patients with ALL (n = 32) and acute myeloblastic leukemia (AML) (n = 12) who, in addition to protocol treatment, underwent transfusion of platelets.

Standard statistics was used for the data analysis.

Conflict of interests. There is no conflict of interests.

3 Results and discussion

All the patients under study were found to have a decreased platelet count in the blood, which was due to the replacement of the megakaryocytic bone marrow lineage with tumor cell clones. It was confirmed by bone marrow examination. The level of platelets in ALL patients ranged from $24 \cdot 10^9/l$ to $107 \cdot 10^9/l$ and averaged $46.0 \pm 17.7 \cdot 10^9/l$. In patients with AML, the platelet count ranged from $42.0 \cdot 10^9/L$ to $73.0 \cdot 10^9/L$ and averaged $55.3 \pm 7.4 \cdot 10^9/L$, that was significantly higher than in ALL patients ($p < 0.05$). The bleeding time in ALL patients was 4.8 ± 1.7 minutes and 6.6 ± 2.3 minutes in AML patients. The prothrombin index in patients of both groups did not differ significantly, and in the majority of patients it was within the norm or exceeded it.

The parameters of autocoagulation test (ACT) in patients with ALL and AML before PCT are presented in *Table. 1*.

According to the ACT in both group of patients, there was an increase in the coagulation potential and a moderate inhibition of fibrinolysis, but there were no significant differences in the parameters in the groups. Permeability of capillaries for water and protein in 14 examined patients did not differ from the normal ones. In 8 patients with a very low level of platelets, an increase in the permeability of capillaries to water was 5.2 ± 1.1 ml (normal level: 2.3 ± 1.8 ml). In patients with AL, the initial state of the hemostasis system was characterized by a decrease in the platelet level, and normal or, in some patients, an elevated plasma factor level of the blood coagulation system indicated compensatory responses. Five patients with severe hemorrhagic syndrome in the onset of the disease were found to have platelet levels below critical values ($< 20 \cdot 10^9/l$), as well as hypocoagulation and activation of fibrinolysis according to ACT (decrease in fibrinogen, prothrombin index, IIT, decrease in fibrinolysis time). There were no significant differences in the parameters of the hemostatic system in patients with ALL and AML before the onset of PCT. It allowed us to include these patients and those, who received thromboconcentrate substitution therapy, into one group.

Modern therapy for acute leukemia includes prolonged high-dose PCT. This leads to the development of numerous complications of hemopoiesis, gastrointestinal tract, immune system, lungs, etc.[9, 13, 14].

Thus, all patients developed severe myelodepression with inhibition of three hematopoietic germs as a result of chemotherapy. The most dangerous is leukopenia (agranulocytosis), which leads to the development of purulent complications, sepsis, infectious-toxic shock (ITS) [5, 14, 15], as well as thrombocytopenia and, as a result, a number of hemostasis disorders and bleeding. The platelets count in 43% of ALL patients decreased due to myelodepression below the critical level ($< 20 \cdot 10^9/L$), in others was not

Table 1

ACT data in patients with ALL and AML before the start of PCT (M±m)

Parameters	A (min)	T1 (min)	T2 (min)	MA (min)	IIT units	Fibrinolysis (min)	Fibrinofen (g/l)	PTI (%)
ACT Patients with AL								
ALL (n=74)	21.7±2.4	3.7±0.5	9.1±1.6	96.5±4.6	2.1±0.2	58.7±4.7	3.1±0.4	97.6±3.7
AML (n=12)	18.2±2.1	3.9±1.0	9.4±0.7	88.7±3.3	1.8±0.2	56.2±2.7	2.4±0.28	89.3±3.1

more than $35 \cdot 10^9/L$. Data of disorders in the hemostasis system secondary to therapy are presented in *Table. 2*.

In 7 patients, long-term and massive bleeding led to severe anemia.

The severity of the condition of patients

Table 2

ACT ($M \pm m$) parameters in patients with AL with myelodepression with and without complications as a result of polychemotherapy

Parameters	A (min)	T1 (min)	T2 (min)	MA (min)	IIT units	Fibrinolysis (min.)	Fibrinogen (g/l)	PTI (%)
ACT Patients with AL								
AL with myelodepression without complications (n = 24)	14.7±3.3	3.63±0.22	8.66±1.12	94.8±2.2	1.92±0.14	54.6±2.3	1.94±0.16	76.6±4.9
AL with myelodepression with complications (n = 49)	11.4±3.1	3.5±0.4	8.28±1.06	88.5±2.6*	1.61±0.12*	51.7±2.8	1.30±0.21*	58.9±3.2*

Note. * significant differences ($p < 0.05$) in parameters of AL patients with myelodepression without complications and with complications.

We compared the parameters of the hemostatic system in patients with AL who received chemotherapy and had no complications except myelodepression with hemostatic parameters of patients with purulent and non-infectious complications.

Patients who did not have severe complications of therapy, were shown to have a moderate decrease in the coagulation potential of the blood, confirmed by a decrease in IIT, MA, as well as activation of fibrinolysis, a decrease in the serum fibrinogen level. The coagulation time was 6.7 ± 1.8 minutes. These changes in the parameters of the hemostasis system did not have its clinical manifestation. There was no hemorrhagic syndrome, and only in certain patients petechiae and mild bleeding were observed in disorders of the integrity of the skin and mucous membranes. Patients with numerous complications, both infectious and non-infectious, had more significant disorders of the hemostatic system, compared with the patients before PCT and patients who did not have numerous complications.

For example, the parameters of the prothrombin index, fibrinogen, IIT were significantly lower ($p < 0.05$), fibrinogen-B, fibrin degradation products were most often detected, A and MA parameter decreased, which indicated the development of disseminated intravascular coagulation syndrome in these patients in phase of consumption. Clinical manifestations were characterized by the development of spontaneous hemorrhages in the skin, mucous membranes, nasal, gastrointestinal, uterine (in girls) bleeding.

depended not only on the degree of myelodepression, but also on its duration and the number of other complications and, above all, infectious ones. The relationship between the severity of disorders of hemostatic parameters, organ and infectious complications in children with oncohematological diseases was presented in a number of studies [15, 16]. An analogous dependence was also determined with the degree of impairment of capillary permeability. The maximal disorders of the permeability of capillaries for water (6.7 ± 1.1 ml/100 ml of arterial blood (normal level: 4.8 ± 0.37) and protein $P\% = 7.8 \pm 0.63\%$, normal level: $4.6 \pm 0.93\%$) were observed in patients with severe complications, multiple organ failure, as well as in patients with myelodepression and critical thrombocytopenia of 7–10 days or more. As a rule, myelodepression with hemorrhagic manifestations was accompanied by a large number of complications.

Our study allowed us to develop a concept of stages of capillarotrophic disorders in patients with acute leukemia. In case of severe prolonged thrombocytopenia, capillary trophism is disrupted, triggering edema and endothelial dysfunction. At this stage, clinical manifestations of capillarotrophic disorders are absent, but laboratory tests detected an increase in the permeability of capillaries to water. Then there was a syndrome of "leakage" of capillaries or extravasations of fluid, electrolytes, protein, other plasma components to interstitial space. The patients were found to have positive water balance during the infusion therapy, relative oliguria, weight gain, edema of tissues, impaired

capillary permeability for protein, progressive hypoproteinemia. Furthermore, there were disorders of Frank-Starling mechanism, a decrease in effective oncotic pressure and an increase in extravasation of the fluid. Administration of plasma, albumin was not very effective at this stage, and the use of diuretics (saluretics) can be unsafe because of deterioration of tissue perfusion and transcapillary exchange. The decrease in blood volume, activation of renin-angiotensin-aldosterone system, antidiuretic hormone and retention of water and sodium in the body were observed. Decrease in blood volume and anemia resulted in disorders of tissue perfusion and oxygen delivery. Then the process progressed and led to organ disorders: edema of the interstitium of soft tissues, internal organs, hypoxia, acidosis. Clinically, it is clearly manifested in the lungs with formation of acute respiratory distress syndrome (ARDS) and in the gastrointestinal tract with formation of stomatogastroenterocolitis, edema, ischemia of the intestinal wall, activation of intestinal microflora, diarrhea. Similar changes develop in all tissues of the body at the stage of transcapillary exchange disruption. Lungs and intestines are a frequent gateway to infection, acting as a pacemaker and promoting the

of the vascular system, preservation of blood volume, transcapillary exchange (capillary permeability, capillarotrophic function of platelets). Secondly, our long-term experience in the treatment of patients with AL children, indicated that in cases of possibility of providing reliable hemostasis, the course and prognosis of the disease improved [17–19]. This fact was confirmed in patients with acute myeloid leukemia (AML), in which the level of blood platelets was maintained at the level of at least $70 \cdot 10^9/L$ by multiple transfusions of platelet concentrate, regulated by the protocol of treatment. None of these patients had severe hemorrhagic syndrome or polyorganic disorders requiring intensive therapy, so better preservation of organs and systems during PCT was registered. This is consistent with research data [15, 20–23] confirming the high efficiency of prevention and treatment of hemorrhagic syndrome in patients with acute leukemia and severe myelodepression. The main variants and incidence of infectious and non-infectious complications in the patients with ALL who did not receive transfusions of platelet concentrate (Group 1) are presented in *Table 3*.

Patients admitted to the intensive care unit were found to have from 3 to 7 complications of PCT (*Table 3*). We have tested the use of donor

Table 3

*Types and incidence of complications of chemotherapy in patients who did not receive transfusions of platelet concentrate **

Non-infectious complications	%	Infectious complications	%
Neutropenia	100	Pneumonia	47
Agranulocytosis	35	(including destructive)	7
Thrombocytopenia $<20 \cdot 10^9/l$	43	Dysbacteriosis of the intestine	17
Bleeding	33	Pneumonia + other infectious foci	11
Hemorrhagic shock	2		
Stage II-III anemia	76	Sepsis	14
Gastrointestinal disorders	21	Other infectious complications (otitis media, pyelonephritis, phlebitis, meningitis)	13
Acute respiratory distress syndrome (ARDS)	33		

*The incidence of complications is expressed in % in relation to the total number of patients with acute leukemia who did not receive transfusions of platelet concentrate.

development of the systemic inflammatory reaction syndrome and sepsis, which reflects the stage of tissue barrier disorders. Diapedesis of blood constituents beyond the vascular system and bleeding are the top of the "iceberg" of capillarotrophic disorders.

The supposition of a significant role of hemostasis system disorders in the development of complications was based on the following factors. Firstly, they are based on the physiological significance of this system in ensuring the aggregate state and viscosity of blood, the integrity

thrombocyte concentrate for the correction of thrombocytopenia and angiotrophic disorders. Thrombocyte concentrate from the donor was obtained with the help of the COBE SPECTRA blood fractionator. It is used to obtain high quality thrombocyte concentrate. Indications for thrombocyte concentrate transfusion were bleeding or thrombocytopenia below the critical level. Bleeding was arrested after 1–2 transfusions of thrombocyte concentrate in all patients, in 36% of patients the platelet count continued to increase, and they quickly recovered from myelodepression

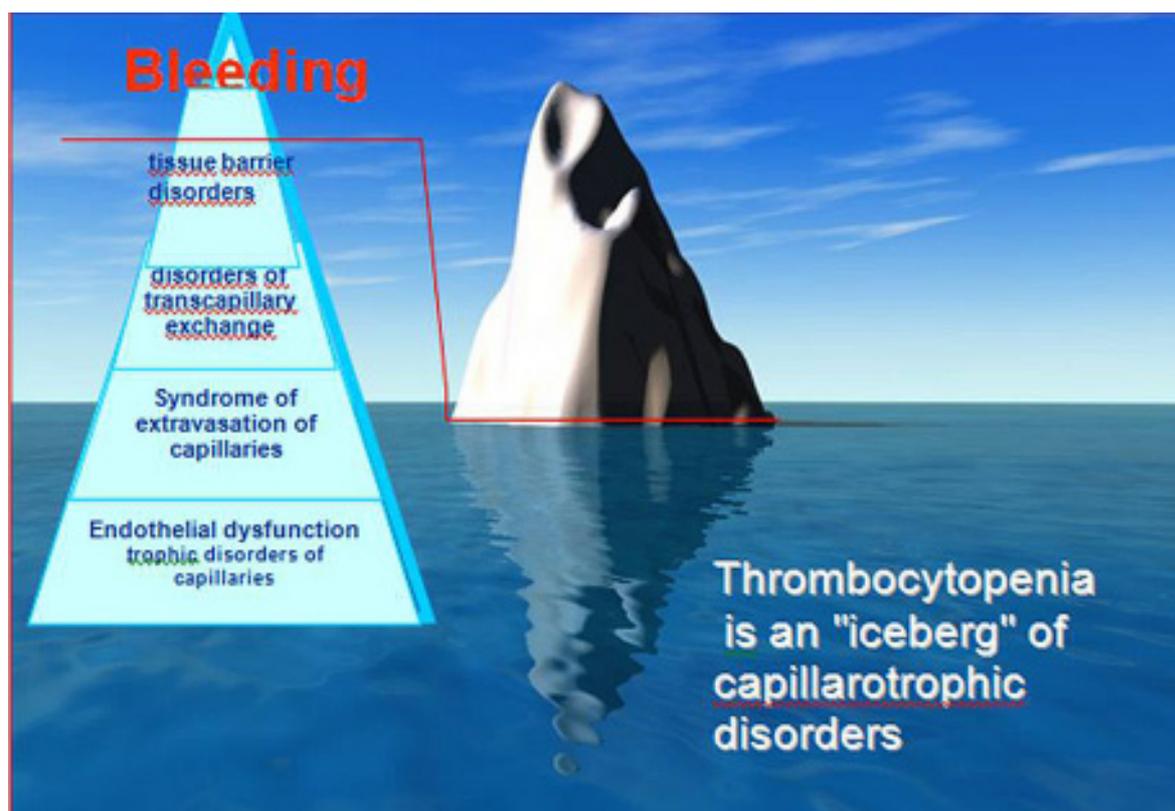


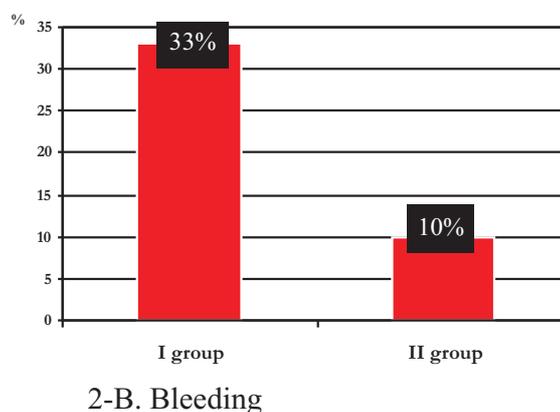
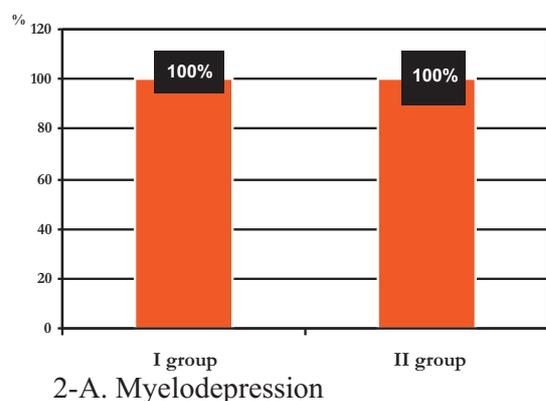
Fig.1. Stages of capillarotrophic disorders in the form of an iceberg with hemorrhagic syndrome as its top

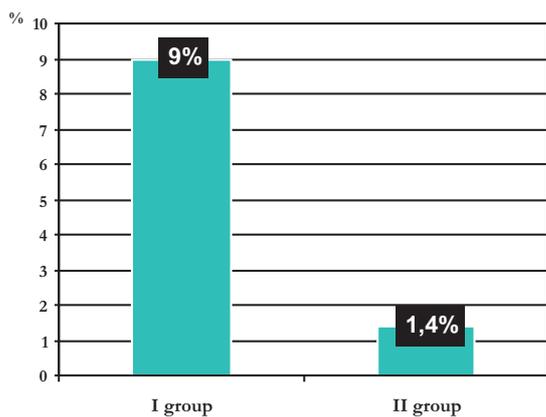
and complications. Moreover, 64% of patients had myelodepression and during the day the platelets again decreased to a critical level. Such patients underwent an intensive course of thrombocyte concentrate replacement therapy (Group 2) daily or at intervals of 1 to 2 days, depending on the therapeutic effect and management of myelodepression.

Evaluation of the effectiveness of thrombocyte concentrate substitution therapy was performed according to clinical data (reduction or elimination of hemorrhagic syndrome and other complications), and by laboratory parameters, blood coagulation time, bleeding time, platelet count, capillary permeability for water and protein, auto-coagulation test, fibrinogen, products

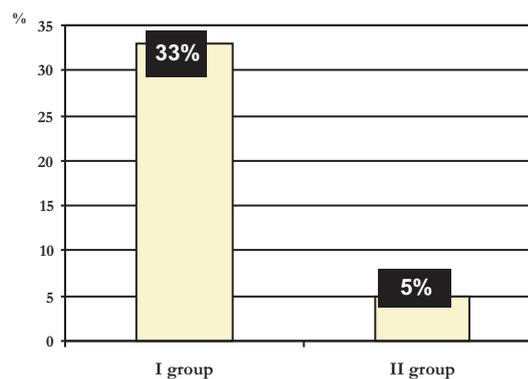
degradation of fibrin, a common protein of blood. The final result of the introduced method of treatment and prevention of complications of PCT was assessed by the number and severity of complications in comparison with patients who were treated without the use of thrombocyte concentrate (group I).

Comparison of the frequency of complications of chemotherapy in patients of Groups 1 and 2 showed that myelodepression is the only complication that was registered with the same frequency (100%), infectious and non-infectious complications were less often observed in Group 2 patients. Thus, bleeding occurred 3.3 times less frequently and there were no cases of hemorrhagic shock, respiratory distress

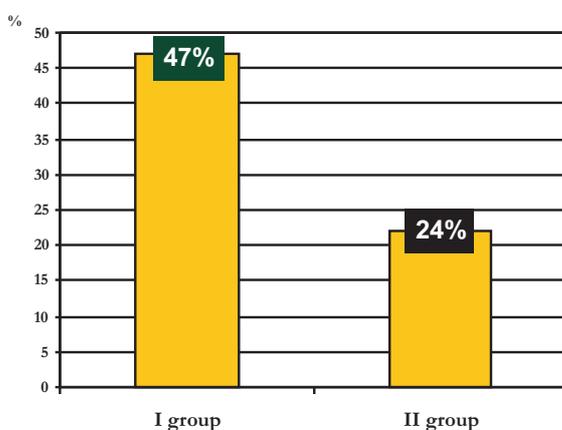




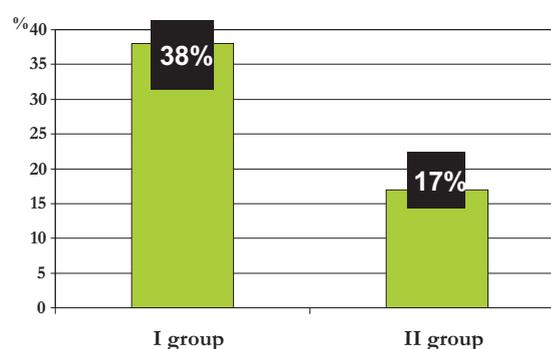
2-C. Sepsis



2-D. ARDS



2-E. Pneumonia



2-F. GIT disorders

Fig. 2. The frequency of complications of chemotherapy in patients of Groups 1 and 2 (the indices are presented as a percentage of the total number of patients in groups)

syndrome (ARDS) was 6.8 times less frequent, dento-esophagogastroenteropathy, enterocolitis was 2 times less frequent, pneumonia was 2.3 times less frequent, sepsis 6 times less often in Group 2. The presented complications in Group 2 patients were less severe and were eliminated earlier in comparison with the patients of the control group.

Mortality at the hospital No. 16 in Kharkov, which was most commonly caused by oncohematological disorders, has decreased over the last 10 years from 2% to 0.2–0.3%.

Conclusions

Patients with AL at the beginning of the disease, before the onset of PCT, were found to have thrombocytopenia, increased plasma clotting factors, normal permeability of capillaries in most children.

Secondary to myelosuppression, critical thrombocytopenia was detected, lasting 7–10 days, accompanied by clinically significant capillarotrophic disorders, which contributed to the development or progression of numerous infectious and non-infectious PCT complications.

Substitution therapy with donor thrombocyte concentrate demonstrated the high effectiveness of treatment of complications of chemotherapy in patients with myelodepression, reduces the frequency and severity of their manifestations.

To prevent the onset and severe course of complications, patients with a critical level of platelets should have preventive, substitution therapy with thromboconcentrate prior to the development of bleeding and capillarotrophic disorders.

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