MedCrave
Step into the World of Research
Hematology & Transfusion International Journal

Research Article
Open Access
CrossMark

# Laboratory rationale for dose reduction anticoagulant for thrombosis complicing treatment patients with hemoblastosis on the background of chemioinduced thrombocytopenia

## Abstract

**Purpose of the study:** To substantiate the minimum hemostatic threshold for platelet count, which regulates the anticoagulant therapy of thrombosis against the background of induced thrombocytopenia in children with malignant neoplasms.

**Material and research methods:** 23 patients (group 1) with hemorrhagic syndrome caused by thrombocytopenia (less than $50 \cdot 10^9$/l) were examined. The control group consisted of 21 patients (group 2) with a similar diagnosis, platelet count less than $150 \cdot 10^9$/l, who did not have bleeding. All examined patients with hemoblastoses had signs of febrile neutropenia. Additionally, under the conditions of a bench experiment, dilutions of platelet donor plasma were prepared with a platelet content of $5.0 \times 10^9$/l, $10.0 \times 10^9$/l, $20.0 \times 10^9$/l, $30.0 \times 10^9$/l, $40.0 \times 10^9$/L, $50.0 \times 10^9$/L, $60.0 \times 10^9$/L, $70.0 \times 10^9$/L, $80.0 \times 10^9$/L, $^9 0.0 \times 10^9$/L, $100.0 \times 10^9$ /l, $200.0 \times 10^9$/l. Platelets were counted in peripheral blood for each sample using an XN-3000 hematology analyzer (manufactured by Sysmex GmbH, Japan) by the impedance method using original reagents (SysmexGmbH). The endogenous thrombin potential (ETP) in patients' platelet plasma was determined by the Hemker method on a Fluoroskanascent fluoroscan manufactured by Thermo Electron Corporation (Maastricht, Netherlands) using reagent kits from Thrombinoscop eBV.

**Research results:** Between the content of platelets in whole blood and EPT of platelet plasma of patients with hemoblastoses, a relationship was revealed, which is reflected by the regression equation: $y = 15.1356 + (0.0745 \cdot x)$, where y is the content of platelets in the blood ($10^9$/l), and x - EPT nM/l·min in venous blood plasma. The minimum threshold value of EPT of platelet plasma, which provides hemostasis, 250 nM/l·min, corresponded to the minimum platelet content of $30.0 \cdot 10^9$/l in the blood of FN patients. Decrease in the content of platelets in donor plasma less than $20 \times 10^9$/l led to a decrease in EPT less than 250 nM/l•min. Between the EPT generated in the platelet donor plasma and the content of platelets in the donor plasma in the range (100.0 -20.0) $\times 10^9$/l, a linear relationship was revealed. When the content of platelets was more than $100.0 \times 10^9$/l, generated by platelet plasma, EPT increased, regardless of the increase in the content of platelets in the plasma under study.

**Conclusion:** in case of thrombosis against the background of chemo-induced thrombocytopenia in the range (100.0 -20.0)$\times 10^9$/l, the patient should receive LMWH at a dose reduced in proportion to the content of platelets in the blood.

**Keywords:** platelet count, coagulation, anticoagulant, heamostasis

Volume 11 Issue 2 - 2023

Vyacheslav Dmitriev
Republican Scientific Center of Pediatric Oncology, Belarus

**Correspondence:** Vyacheslav Dmitriev, Republican Scientific Center of Pediatric Oncology, Belarus,
Email dmitrievhaemato@mail.ru

**Received:** February 20, 2023 | **Published:** April 10, 2023

## Introduction

Thrombosis is one of the most frequent complications of cancer and the second leading cause of death among patients with malignant neoplasms[1,2] including children.[3,4] According to the unanimous opinion of leading experts in the field of onco-hematology, the use of low molecular weight heparins (LMWH), both in adults and children, is recognized as the "gold" standard of antithrombotic therapy. The clinical features of the underlying disease and chemotherapy in some cases lead to hypocoagulation changes and thrombocytopenia, which requires a reduction in the therapeutic dose of the anticoagulant, and in some cases, hemostatic replacement therapy.

The Committee for Standardization of the International Society on Thrombosis and Haemostasis (ISTH, International Society on Thrombosis and Haemostasis[5] proposed in case of thrombocytopenia in subacute or chronic 50% therapeutic dose of LMWH, or switch to prophylactic doses of anticoagulants at a platelet count of (50.0-25.0) x $10^9$/l. When the number of platelets is less than $25.0 \times 10^9$/l, the administration of LMWH is stopped, the transfusion of donor platelet concentrate is performed, after which the administration of LMWH is resumed at a prophylactic or therapeutic dose. Recommendations regulating the hemostatic threshold of blood platelets in most cases do not have an evidence base, they are based on clinical experience and the opinion of leading experts in the field of transfusiology.[6–8]

**Purpose of the study:** To substantiate the minimum hemostatic threshold for platelet count, which regulates the anticoagulant therapy of thrombosis against the background of induced thrombocytopenia in children with malignant neoplasms.

## Material and research methods

23 patients (group 1) with hemorrhagic syndrome (nasal, gastrointestinal, bleeding from the oral mucosa) were examined.

The group included patients in whom thrombocytopenia (less than $50\times10^9$/l) was one of the main causes of bleeding. As a control, 21 patients (Group 2) with a similar diagnosis, platelet count less than $150\times10^9$/l, who did not have bleeding and did not receive hemostatic replacement therapy during the day preceding inclusion in the study, were examined. All 44 examined patients on the background of neutropenia (the number of granulocytes is less than $0.5\times10^9$/l) had febrile fever (> 38.5°C at least 2 times a day on the day of the study). The nosological structure of the groups is presented in Table 1.

**Table 1** Nosological structure of patients with hemoblastoses

| | Gem syndrome | |
|---|---|---|
| **Nosological characteristics of onco-hematological diseases** | **Yes Group 1 N=23** | **No Group 2 N=21** |
| ALL T1, number of patients | 2 | 2 |
| ALL T2, number of patients | 4 | 4 |
| AML M1, number of patients | 2 | 1 |
| AMLM2, number of patients | 1 | 0 |
| AML M5, number of patients | 2 | 1 |
| AML M7, number of patients | 1 | 1 |
| CNS tumor, patients | 2 | 4 |
| Neuroblastoma, patients | 4 | 2 |
| Lymphoma, number of patients | 4 | 6 |
| Ovarian teratoma, patients | 1 | 0 |

Venous blood for the study of coagulation in a volume of 5 ml was collected by puncture of a peripheral vein without applying a tourniquet, stabilized with a 3.8% solution of sodium citrate in a ratio of $^9$:1, respectively. The stabilized blood was centrifuged at 20-22°C at 200g for 10 minutes to obtain platelet rich plasma, after which a portion of the platelet plasma was used to perform a thrombin generation test. The remaining platelet plasma was further centrifuged at 2000g for 10 minutes to prepare lean (platelet-free) plasma used for coagulation studies.

The study of coagulation included: registration by the turbidimetric method of chronometric indicators (activated partial thromboplastin time - APTT, prothrombin time - PT, thrombin time - PT), plasma fibrinogen content by the Claus method using automatic coagulometers ACL-7000 and ACL-9000 from InstrumentationLaboratory (IL) with using IL diagnostic kits. Presentation of the results of chronometric tests in the form of a relative value (R), equal to the ratio of the studied chronometric indicator to the value of the corresponding indicator of the control plasma, made it possible to compare the results, regardless of the time of the study and the activity of the reagents used. Based on the result of determining the prothrombin time, taking into account the sensitivity of the reagent, the analyzer automatically calculated the activity of the factors of the prothrombin complex and the international normalized ratio (INR). For the value of hemostasis indicators, reflecting the age norm, the results of observations presented in the publications were used.[9,10]

To answer the question about the relationship between the platelet content and the endogenous thrombin potential generated by platelet plasma, a bench experiment was conducted to register EPT of platelet donor plasma with different levels of platelets. After obtaining informed consent for the examination before the upcoming preparation, the venous blood of 10 donors was stabilized with sodium citrate at a temperature of 20-22°C, centrifuged for 5 minutes at 200g, after which the platelet-rich plasma was transferred into a plastic dish. The rest of the blood was centrifuged with 2000 g for 20 minutes. Platelet-poor plasma was collected in a separate plastic dish and used to prepare a series of dilutions of platelet plasma. Dilutions of platelet plasma were prepared with a platelet content of $5.0\times10^9$/l, $10.0\times10^9$/l, $20.0\times10^9$/l, $30.0\times10^9$/l, $40.0\times10^9$/l, $50.0\times10^9$/l, $60.0\times10^9$/l, $70.0\times10^9$/L, $80.0\times10^9$/l, $90.0\times10^9$/l, $100.0\times10^9$/l, $200.0\times10^9$/l. For each series of platelet plasma dilutions, 10 determinations of the endogenous thrombin potential were made.

The endogenous thrombin potential of platelet plasma was determined by the Hemker method on a Fluoroskanascent fluoroscan manufactured by Thermo Electron Corporation (Maastricht, Netherlands) using reagent kits from Thrombinoscope BV. On a 96-well plate ThrombinoscopeBV (Maastricht, Netherlands), 80 µl of the studied platelet plasma was added to the first 4 wells. In the first 2 wells, 20 µl of PRP reagent (Cat No. TS42.00) containing a mixture of 0.5 pM solution of tissue factor and phospholipids was added. Thrombin Calibrator (Cat No. TS20.00) was added to the second 2 wells. The reaction was initiated after the automatic addition of 20 µl of a mixture of 2.5 mM fluosubstrate in 0.1 M calcium chloride solution (FluCa kit, cat no. TS50.00) on board Fluoroskanascent. All manipulations were performed in accordance with the instructions for the reagent kits and the instructions for working on Fluoroskanascent.

Platelet counting for each whole blood sample and donor plasma in a series was carried out on an XN-3000 hematological analyzer (manufactured by SysmexGmbH, Japan) by the impedance method using original reagents (SysmexGmbH). At the same time, the content of platelets in platelet plasma was monitored using a microscope with a phase-contrast attachment using the method of G. Brecheretal (1953).

Statistical data analysis was performed using Statistical programs (version 6.0). To assess the degree of significance of differences between the compared groups, a two-tailed nonparametric Mann-Whitney test was used. The relationship between the change in the values of the analyzed indicators was assessed by the criterion of rank correlation R (Spearmen). When assessing the significance of differences, a threshold of values for $p<0.05$ was used.

## Research results

Blood coagulation parameters in patients with bleeding differed from the corresponding control values (Table 2). The most significant difference in patients with bleeding was an increase in APTT to 34.7 (25.0-54.0) s, compared ($p=0.03$) with control 31.0 (25.4-37.0) s.

**Table 2** Blood coagulation of patients with bleeding and in control, median (10th - 90th) percentiles

| Analyzed feature | Gem syndrome | | Mann-Whitney U-test |
|---|---|---|---|
| | Yes group 1 N=23 | No group 2 N=21 | P(1-2) |
| Activated partial thromboplastin time (APTT),s | 34,7 | 31,0 | 0,030 |
| APTT ratio patient / control, units | (25,0-54,0) | (25,4-37,0) | |
| | 1,1 | 0,9 | 0,01 |
| | (0,85-1,6) | (0,8-1,1) | |
| International normalized ratio, units | 1,2 | 1,03 | 0,021 |
| | (0,95-1,5) | 0,87-1,25 | |
| Factor activity | 76,0 | 94,0 | 0,025 |
| prothrombin complex,% | (66,0-108,0) | (70,0-128,0) | |
| Thrombin time (TT), s | 19,5 | 17,5 | 0,21 |
| | (14,0-35,0) | (14,7-23,0) | |
| TT ratio patient / control, units | 1,28(0,78-1,8) | 1, 2(0,87-1,5) | 0,22 |
| Blood fibrinogen, g/l | 3,0 (1,5-6,9) | 3,6 (1,7-5,2) | 0,63 |
| whole blood platelets , $\times 10^9$/л | 28,0 | 74,5 | 0,0001 |
| | (11,0-49,0) | (15,0-113,0) | |
| Endogenous thrombin potential of platelet plasma, nM/l • min | 123,0 | 645,0 | 0,00001 |
| | (22,0-424,0) | (284,0-932,0) | |

**Note:** P is the significance of the difference in indicators in patients with bleeding (1) and without (2) bleeding, U-test.

In patients with bleeding, despite the hypocoagulation direction of the changes, compared with the control, the parameters of the plasma coagulation link could not be an independent cause of bleeding. Among the 44 examined patients, no relationship was found between the fact of bleeding and changes in coagulation parameters. A correlation was found between the decrease in platelet count (R= - 0.50; p=0.000548) and the fact of bleeding. A closer relationship was found between the fact of hemorrhagic syndrome and a decrease in platelet plasma EPT (R= - 0.79; p=0.000001) to 123.0 (22.0-424.0) nM/l•min in patients with bleeding according to compared with 645.0 (242.0-999.0) nM/l•min in children without bleeding. In patients with bleeding, the median blood platelet count was $28.0\times10^9$/L, and the 90th percentile value was $50\times10^9$/L (Figure 1). In patients without bleeding, the content of peripheral blood platelets varied from $15.0\times10^9$/l to $125.0\times10^9$/l.

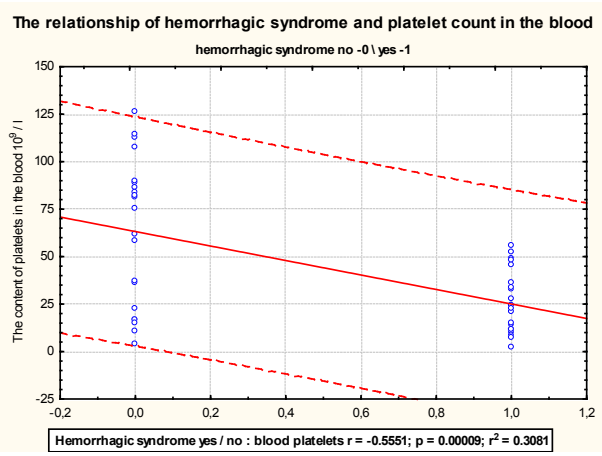


**Figure 1** The relationship between the content of platelets in the blood hemorrhagic syndrome (no -0, yes -1).

More distinct differences between the groups (hemsyndrome - yes / no) were registered when using as a diagnostic criterion the indicator of endogenous thrombin potential (EPT) generated in the platelet plasma of patients. There was no hemorrhagic syndrome in any patient of the second group with platelet plasma EPT value of more than 250.0 nM/l•min.

The EPT value less than 500.0 nM/l•min, Figure 2 was registered in the vast majority of patients of the first group with bleeding. In patients with bleeding, the median EPT of platelet plasma was 123.0 nM/l·min, and the value of the 90th percentile did not exceed 500 nM/l·min. Between the content of platelets in whole blood and the EPT of platelet plasma, a relationship was revealed. Figure 3 which is reflected by the regression equation: $y = 15.1356 + (0.0745 \cdot x)$, where y is the content of platelets in the patient's peripheral blood ($10^9$/l), and x - EPT nM/l·min of the patient's platelet plasma. Knowing the minimum threshold value of EPT, which provides hemostasis of 250 nM/l·min, it is possible to calculate the required minimum platelet count in peripheral blood.

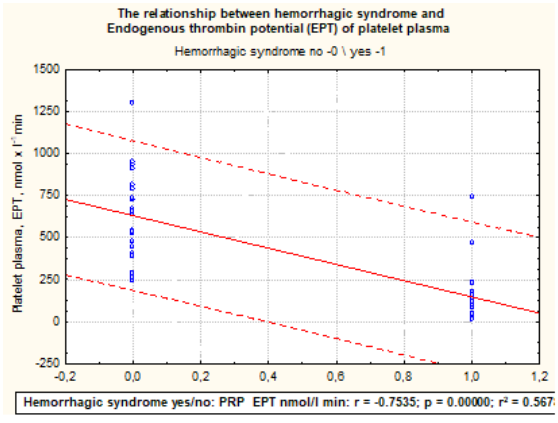


**Figure 2** The relationship of the endogenous potential of platelet thrombin plasma and hemorrhagic syndrome (no -0, yes -1).

**Citation:** Dmitriev V. Laboratory rationale for dose reduction anticoagulant for thrombosis complicing treatment patients with hemoblastosis on the background of chemioinduced thrombocytopenia. *Hematol Transfus Int.* 2023;11(2):35–39. DOI: 10.15406/htij.2023.11.00298

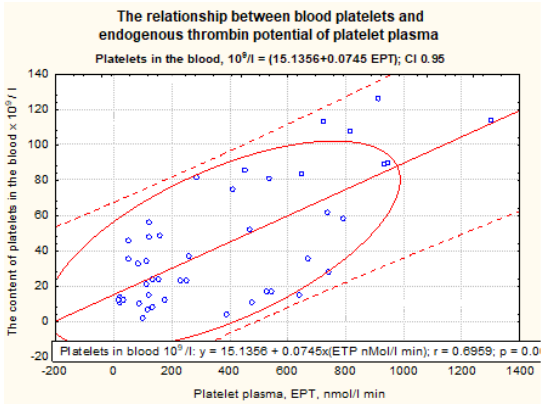


**Figure 3** Endogenous potential of thrombin in platelet plasma and platelet count in whole blood patients with hemoblastoses.

For example, the minimum content of platelets in the blood (y), which provides protection against bleeding, will be: y = (15.1356 + 0.0745 · 250 = 33.76) 30·10⁹/l. Hemsyndrome was not registered in the vast majority of patients with platelet plasma EPT value of more than 500 nM/l•min, which corresponded to the calculated platelet content in whole blood (y = 15.1356 + 0.0745 · 500 = 52.39) 50·10⁹/ l.

The results of the bench experiment showed that the lowest ability to generate thrombin 117.0 (81.0-159.0) nM/l•min was registered in donor plasma containing platelets at a concentration of 5.0•10⁹/l. The maximum ability of platelet plasma to generate thrombin in the amount of 1105.0 (780.0-1820.0) nM/l•min was registered in platelet-rich plasma with a platelet content of 406.0 (376.0-570.0)•10⁹/l. At a platelet count of 100.0•10⁹/l, the EPT value of 925.0 (743.0-1500.0) nM/l•min differed little (p=0.35; T-test) from the EPT of 1066.0(781, 0-1450.0) nM/l•min at a platelet count of 200.0•10⁹/l, or from the EPT value of 1105.0(780.0-1820.0) nM/l•min (p=0.25; T-test), registered at the content of platelets 406.0 (376.0-570.0)•10⁹/l.

At a platelet count of (5.0-10.0)•10⁹/l, the EPT value of 142.0 (114.0-226.0) nM/l•min was less than the threshold value of 250 nM/l•min, and the ratio of EPT/ platelets significantly differed (p=0.01) from that at the content of platelets 20.0×10⁹/l. In the range (20.0-100.0)•10⁹/l, a linear relationship was found between the content of platelets and the ability of platelet plasma to generate thrombin (EPT) (Figure 4). The presence of a linear dependence was confirmed by the coefficient of the ratio of the value of EPT to the content of platelets for each of the series of dilution of platelets in platelet plasma (Table 3).

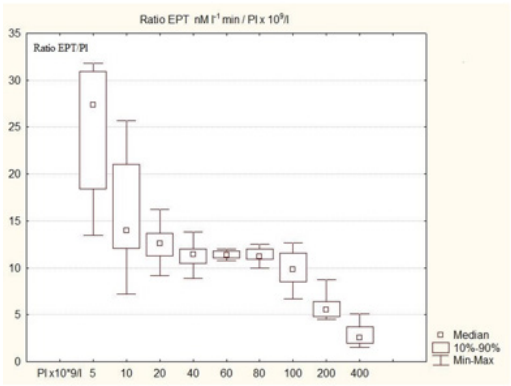


**Figure 4** Relationship between EPT and platelet count *In Vitro*.

**Table 3** Endogenous potential of thrombin in platelet plasma depending on the content of platelets, median (10th - 90th) percentile

| No. Series | Analyzed feature: Dilution of platelet plasma ·10⁹/л for each series n=10 | Real content platelets (PL), ·10⁹/л for each series n=10 | Endogenous Potential Thrombin (EPT), nM/l•min for each series n=10 | Attitude EPT /TR, for each series n=10 |
|---|---|---|---|---|
| 1 | 5,0 ·10⁹/l | 6,0 (5,5-6,5) | 117,0 (81,0-159,0) | 27,4 (13,5-31,0) P1-3= 0,01 * |
| 2 | 10,0 ·10⁹/l | 10,0 (9,0-12,0) | 142,0 (114,0-226,0) | 14,0(12,0-22,0) P2-3= 0,72 |
| 3 | 20,0 ·10⁹/l | 19,0 (17,0-21,0) | 232,0 (187,0-251,0) | 12,6 (9,2-16,0) |
| 4 | 30,0 ·10⁹/l | 31,0 (26,0-32,0) | 310,0 (287,0-451,0) | 10,9(9,2-12,0) P4-3= 0,72 |
| 5 | 40,0 ·10⁹/l | 40,0 (36,0-42,0) | 353,0 (321,0-456,0) | 11,5 (9,1-12,8) P5-3= 0,07 |
| 6 | 50,0 ·10⁹/l | 47,0 (44,0-52,0) | 580,0 (486,0-820,0) | 11,5(10,0-13,6) P6-3= 0,72 |
| 7 | 60,0 ·10⁹/l | 58,0 (55,0-63,0) | 700,0 (680,0-720,0) | 10,0 (9,0-14,5) P7-3= 0,72 |
| 8 | 70,0 ·10⁹/l | 68,0 (63,0-75,0) | 753,0 (593,0-1165,0) | 12,0 (8,0-14,5) P8-3= 0,72 |
| 9 | 80,0 ·10⁹/l | 80,0 (77,0-83,0) | 917,0 (815,0-987,5) | 11,2 (10,0-12,5) P9-3= 0,62 |
| 10 | 90,0 ·10⁹/l | 90,0 (86,0-95,0) | 983,0 (915,0-1165,0) | 11,0 (9,5-13,0) P10-3= 0,45 |
| 11 | 100,0 ·10⁹/l | 97,0 (87,0-102,0) | 998,0 (843,0-1500,0) | 9,8 (8,3-11,7) P11-3= 0,29 |
| 12 | 200,0 ·10⁹/l | 197,0 (181,0-209,0) | 1066,0 (781,0-1450,0) | 5,5(4,5- 8,1) P12-3= 0,01* |
| 13 | Platelet rich plasma | 406,0 (376,0-570,0) | 1105,0 (780,0-1820,0) | 2,5(1,5-5,1) P13-3= 0,04 * |

**Citation:** Dmitriev V. Laboratory rationale for dose reduction anticoagulant for thrombosis complicing treatment patients with hemoblastosis on the background of chemioinduced thrombocytopenia. *Hematol Transfus Int.* 2023;11(2):35–39. DOI: 10.15406/htij.2023.11.00298

## Discussion

Hemorrhagic complications in 20 out of 23 patients with chemo-induced thrombocytopenia on the background of FN occurred when the ability of platelet plasma to generate thrombin was less than 250 nM/l•min. The minimum hemostatic threshold for the content of platelets in the blood, in accordance with the regression equation, was (y = 15.1356 + (0.0745 · 250) = 33.76) 30·10$^9$/l. When the value of EPT platelet plasma more than 500 nM/l•min bleeding practically did not occur. The threshold value of the platelet content, taking into account the regression equation, approached (y = 15.1356 + (0.0745 · 500) = 52.39·10$^9$/l) to 50·10$^9$/l. The obtained results explain the need for prophylactic transfusion of donor platelets in patients with febrile neutropenia when the platelet count in peripheral blood is less than 30·10$^9$/l. Therefore, if in the event of thrombosis a patient with FN would receive LMWH, the anticoagulant should be discontinued when the number of platelets in the blood falls below 30·10$^9$/l.

The minimum hemostatic threshold of EPT 250 nM/l•min in the bench experiment was registered taking into account the 90th percentile for the value of EPT 232.0 (187.0-251.0) nM/l•min with the number of platelets in donor plasma within 20.0•10$^9$/l. The EPT value of 250 nM/l•min reflected the hemostatic minimum of platelets in platelet plasma 20.0•10$^9$/l, below which bleeding is possible, and the patient without signs of FN needs replacement transfusion of donor platelets.

A decrease in the EPT value of platelet plasma in parallel with a decrease in the content of platelets in the range (100.0-20)•10$^9$/l is accompanied by inhibition of thrombin generation in platelet plasma in proportion to the degree of thrombocytopenia. This circumstance indicates the need, in the case of antithrombotic treatment, to reduce the therapeutic dose of LMWH in proportion to the degree of thrombocytopenia with a decrease in the platelet count in the blood of less than 100.0•10$^9$/L.

A decrease in the content of platelets in blood plasma to 20 x 10$^9$/l or less leads to a decrease in EPT less than 250 nM/l x min, which increases the risk of bleeding associated with thrombocytopenia. In this case, it is necessary to foresee the potential need for transfusion of donor platelets in a patient with progressive chemo-induced thrombocytopenia. If the patient has had thrombosis, then progressive thrombocytopenia with a decrease in the number of platelets less than 20 x 10$^9$/l will require discontinuation of the anticoagulant in order to avoid bleeding.

When the content of platelets is more than 100.0•10$^9$/l, generated by platelet plasma, EPT increased, regardless of the increase in the content of platelets in the plasma under study. Therefore, in the event of thrombosis, the patient can receive the full therapeutic dose of the anticoagulant. In addition, any surgical intervention can be performed on the patient without additional platelet transfusion.

Thus, comparison of the platelet count in whole blood with the EPT of platelet plasma made it possible to substantiate the regimen for reducing the daily dose (or canceling) of the anticoagulant depending on the platelet count in the blood in patients with thrombosis and to determine the threshold value of thrombocytopenia, upon reaching which transfusion is indicated.

**Donor platelets:**

In the case of thrombosis, which complicates the treatment of patients with malignant neoplasms, with a platelet count of more than 100.0•10$^9$/l, the use of anticoagulants in a therapeutic dose is justified A decrease in the platelet count in the range from 100.0 x 10$^9$/l to 20 x 10$^9$/l is accompanied by inhibition of thrombin generation in platelet plasma in proportion to the degree of thrombocytopenia. In the case of the use of anticoagulants in patients with thrombosis, it is necessary to reduce the therapeutic dose of LMWH in proportion to the decrease in the concentration of platelets in the blood. In patients with thrombosis without signs of SIRS, with a decrease in the content of platelets in the blood of less than 20.0×10$^9$/l, anticoagulant withdrawal is indicated to prevent bleeding. The use of anticoagulants can be resumed after a replacement transfusion of donor platelets with an increase in the platelet count in the blood of more than 20.0 x 10$^9$/l. During chemotherapy, to protect against bleeding in patients with signs of FN, platelet transfusion should be considered when the platelet count in the blood falls below 30·10$^9$/L.

## Acknowledgments

None.

## Conflicts of interest

The author declares that there is no conflict of interest.

## Funding

None.

## References

1. Campbell PM, Ippoliti C, Parmar S. Safety of anticoagulation in thrombocytopenic patients with hematologic malignancies: a case series. *J Oncol Pharm Pract*. 2017;23(3):220–225.
2. Mantha S, Miao Y, Wills J, et al. Enoxaparin dose reduction for thrombocytopenia in patients with cancer: a quality assessment study. *J Thromb Thrombolysis*. 2017;43(4):514–518.
3. Kopolovic I, Lee AY, Wu C. Management and outcomes of cancer-associated venous thromboembolism in patients with concomitant thrombocytopenia: a retrospective cohort study. *Ann Hematol*. 2015;94(2):329–336.
4. Khanal N, Bociek RG, Chen B, et al. Venous thromboembolism in patients with hematologic malignancy and thrombocytopenia. *Am J Hematol.* 2016;91(11):E468–E72.
5. Carrier M, Khorana AA, Zwicker JI, et al. Management of challenging cases of patients with cancerassociatedthrombosis including recurrent thrombosis bleeding: guidance from the SSC of the ISTH: a reply to a rebuttal. *J ThrombHaemost.* 2014;12(1):116–117.
6. Babilonia KM, Golightly LK, Gutman JA, et al. Antithrombotic therapy in patients with thrombocytopenic cancer: outcomes associated with reduced-dose, low-molecular-weight heparin during hospitalization. *Clin Appl Thromb Hemost.* 2014;20(8):799–806.
7. Delluc A, Le Gal G, Scarvelis D, Carrier M. Outcome of central venous catheter associated upper extremity deep vein thrombosis in cancer patients. *Thromb Res*. 2015;135(2):298–302.
8. Lise J, Estcourt, Janet Birchall, et al. Guidelines for the use of platelet transfusions. *Br J Haematol.* 2017;176(3):365–394.
9. Andrew M, Vegh P, Johnston M, et al. Maturation of the hemostatic system during childhood. *Blood.* 1992;80(8):1998–2005.
10. Toulon P, Berruyer M, Brionne-Franqois M, et al. Age dependency for coagulation parameters in paediatric populations. *Thromb Haemost*. 2016;116(1):9–17.