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Centromere and Genome Instability in Patients with Acute Leukemia

Sirenko Artur*

Department of Biology and Ecology, Vasyl Stefanyk Precarpathian National University, Ivano-Frankivsk, Ukraine

ABSTRACT

The phenomena of Premature Centromere Division (PCD) of metaphase chromosomes and premature anaphase (C-anaphase) in 57 patients with Acute Lymphoblastic Leukemia (ALL) and 32 patients with Acute Myeloblastic Leukemia (AML) were investigated. It was found that the levels of PCD and C-anaphase in patients with acute leukemia in the first acute period of the course of the disease in both peripheral blood and red bone marrow significantly exceed these indicators in the control group (healthy blood and red bone marrow donors). During the period of remission, the values of PRC and C-anaphase decreased and approached the values of the control group. The phenomena of PRC and C-anaphase can be used as additional non-specific diagnostic criteria for the course of ALL and AML. A high positive correlation was found between the level of blasts in peripheral blood and the level of PCD in peripheral blood (r=0.890 for ALL, r=0.987 for AML), which suggests that this phenomenon is characteristic to a greater extent of blast cells than of normal lymphocytes. A relationship was revealed-a high positive correlation between the level of aneuploid clones in the peripheral blood of patients with acute leukemia and the level of PCD in the peripheral blood (r=0.832 for ALL; r=0.960 for AML), which suggests that PCD is one of the causes of instability of the genome in acute leukemia's.

Keywords: Leukemia; Centromere; Oncogenesis; Genome

INTRODUCTION

One of the problem of the pathogenesis of acute leukemia's is the problem of instability of the genome of cells: The more unstable the genome of red bone marrow cells, the greater the probability of the appearance of a leukemic clone of cells. Additional secondary mutations of cancer cells (including aneuploid ones) increase their aggressiveness. Clarifying the reasons for the instability of the genome of red bone marrow cell clones is an important aspect of research into the causes of the pathogenesis of acute leukemia's. In this work, the phenomena of premature separation of centromeres (PCD) of metaphase chromosomes and premature anaphase (C-anaphase) are investigated from the point of view of their use for the diagnosis of acute leukemia's and clarification of their role in the instability of cell genomes. The phenomena of PCD and C-anaphase were discovered back in the 1960s, but for some time they were considered artifacts of *in vitro* cell culture. But later numerous studies proved that these phenomena are manifested at a high level in various pathologies, including cancer, including acute leukemia [1-22]. Fitzgerald P was one of the first researchers who proved that the phenomena of PRC and C-anaphase are not random, but related to certain pathologies [7]. Mehes and Kosztolanyi demonstrated that the PRC phenomenon is associated with genome instability [15,16]. Moorhead and Heyman showed that the PRC phenomenon is observed in Alzheimer's disease [18]. And although the centromere has been studied for a long time and thoroughly [4], the molecular mechanisms of the PCD and C-anaphase phenomena still remain unexplored.

MATERIALS AND METHODS

57 children with Acute Lymphoblastic Leukemia (ALL) and 32 children with Acute Myeloblastic Leukemia (AML) were studied. The research was conducted in the Lviv Regional Specialized

Correspondence to: Sirenko Artur, Department of Biology and Ecology, Vasyl Stefanyk Precarpathian National University, Ivano-Frankivsk, Ukraine, E-mail: bratlibo@yahoo.co.uk

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Clinical Hospital (Ukraine) in 1991-2023. Cell cultures of peripheral blood and red bone marrow taken in the first acute period before the start of treatment were studied. The diagnoses of all patients were confirmed on a Bacton Dickinson flow cytometer. Healthy blood and red bone marrow donors were studied as a control group. Cell cultures were created as standard using Eagle's medium and RPMI-1640 from Life Technologies and Sigma, fetal bovine serum from Biomark Ink, and L-glutamine from Sigma. Peripheral blood cells were stimulated with phytohemagglutinin (PhHA) from Difco. The culture of red bone marrow cells was created without mitogen stimulation. When red bone marrow cells were cultivated, no mitogen was added. Cells were cultured for 72 hours at a temperature of 37°C, treated with a hypotonic solution of KCl, and fixed with a mixture of ethanol and acetic acid (3:1). Chromosome preparations were routinely stained with Giemsa stain. They were analyzed microscopically using a Leitz microscope. Blood and bone marrow donors who underwent examination were used as a control group. The phenomenon of PCD is understood as a phenomenon in which from 1 to 10 chromosomes per cell show premature separation of centromeres. And C-anaphase is a phenomenon in which all the chromosomes of a cell show premature separation.

RESULTS

As a result of the research, it was found that the levels of PCD and C-anaphase in patients with acute leukemia both in the Peripheral Blood (PB) and in the red Bone Marrow (BM) were statistically significantly different from the levels of PCD and C-anaphase in the control group and during the remission period in patients with Acute Lymphoblastic Leukemia (ALL), the levels of PCD and C-anaphase decreased and approached the values of the control group (Table 1) (Figures 1 and 2).

Group	PCD		C-anaphase	
	PB	BM	PB	BM
ALL I acute period	29.16 ± 3.48	31.70 ± 3.59	7.63 ± 1.5	9.58 ± 1.5
AML I acute period	18.06 ± 4.12	28.09 ± 4.58	5.13 ± 3.87	7.19 ± 2.24
ALL remission	3.4 ± 0.3	3.5 ± 0.4	1.5 ± 0.3	0
Control group	1.7 ± 0.3	3.0 ± 0.3	0	0

Table 1: Levels of PRC and C-anaphase in patients with acute leukemia (in the first acute period and in the period of remission) and in the control group.

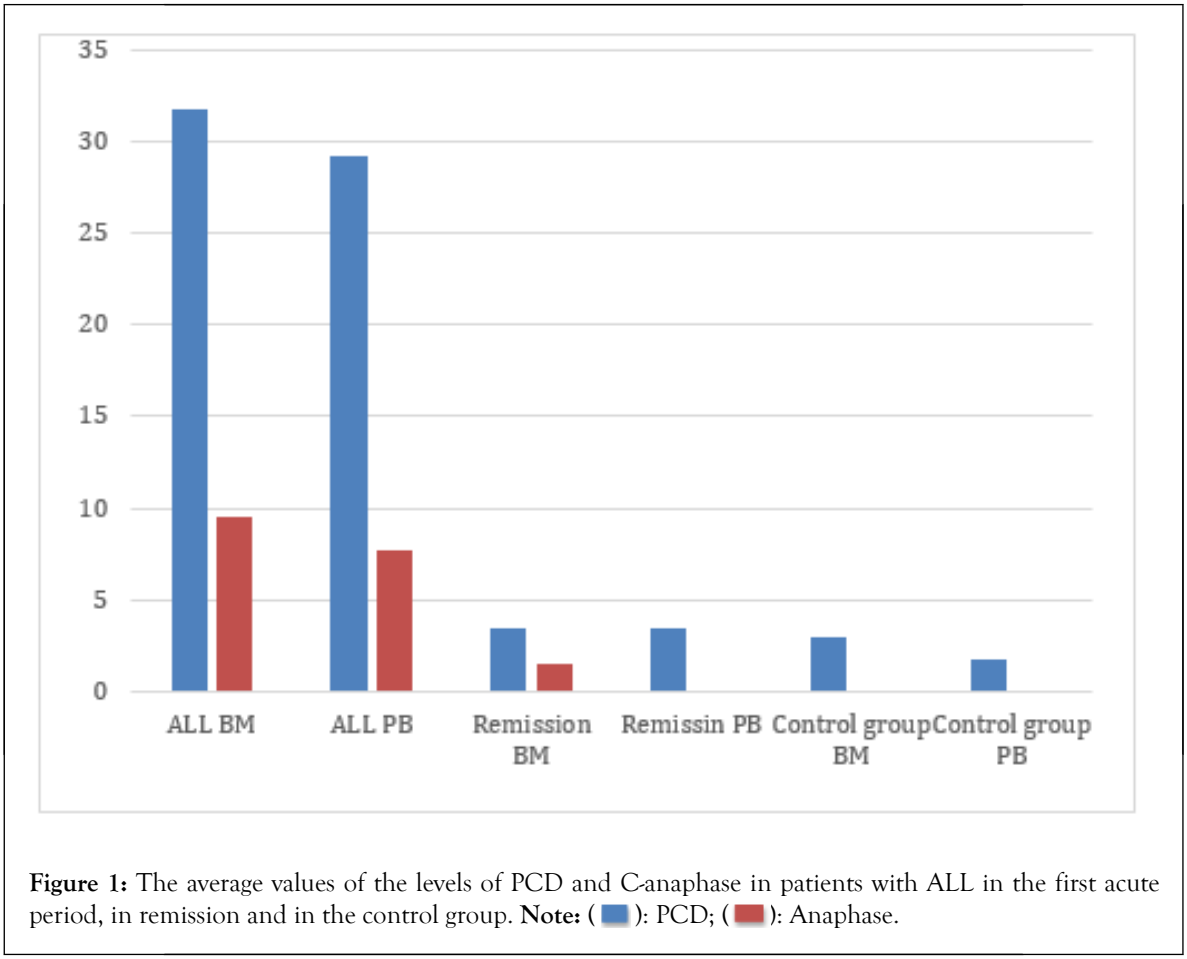

Figure 1: The average values of the levels of PCD and C-anaphase in patients with ALL in the first acute period, in remission and in the control group. **Note:** ( ): PCD; ( ): Anaphase.

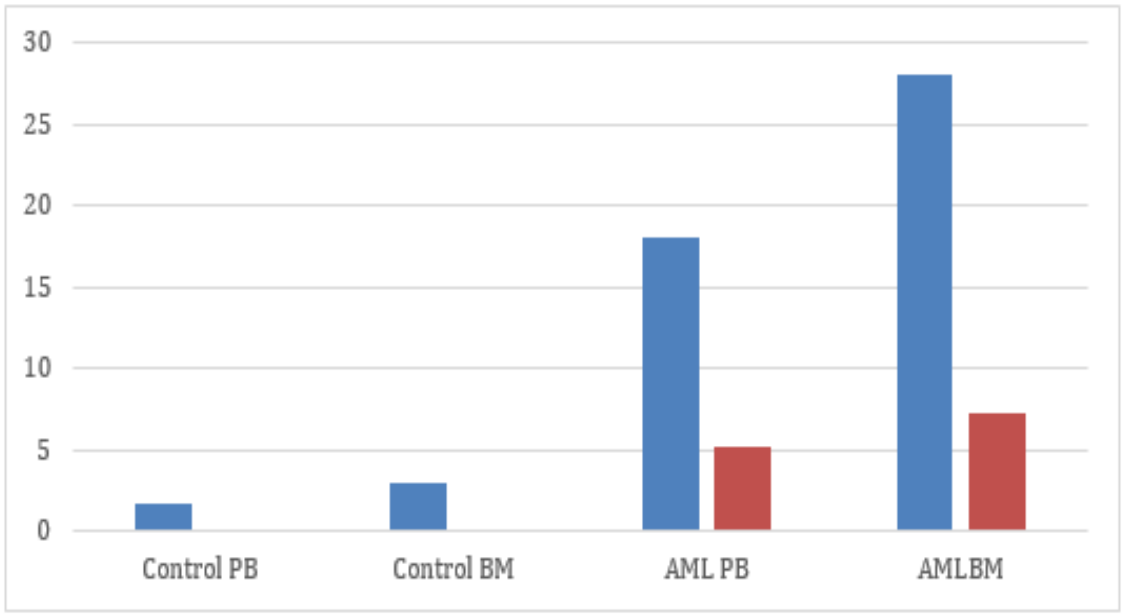

Figure 2: Levels of PCD and C-anaphase in Peripheral Blood (PB) and Bone Marrow (BM) in patients with AML in the first acute period and in the control group. **Note:** ( ): AML; ( ): PB.

The obtained results allow us to propose the phenomena of PCD and C-anaphase as an additional diagnostic criterion for acute leukemia's. The relationship between the phenomena of PCD, C-anaphase and various clinical parameters of acute leukemia's was studied. No correlation was found with such parameters as the level of hemoglobin, the level of platelets in patients with acute leukemia, but a high positive correlation was found between the level of blasts in peripheral blood and the level of PCD in peripheral blood (r=0.890) in patients with acute lymphoblastic leukemia, a high positive correlation was found between the level of blasts in the peripheral blood and the level of PCD in the red bone marrow (r=0.896) in patients with acute lymphoblastic leukemia (Figures 3 and 4).

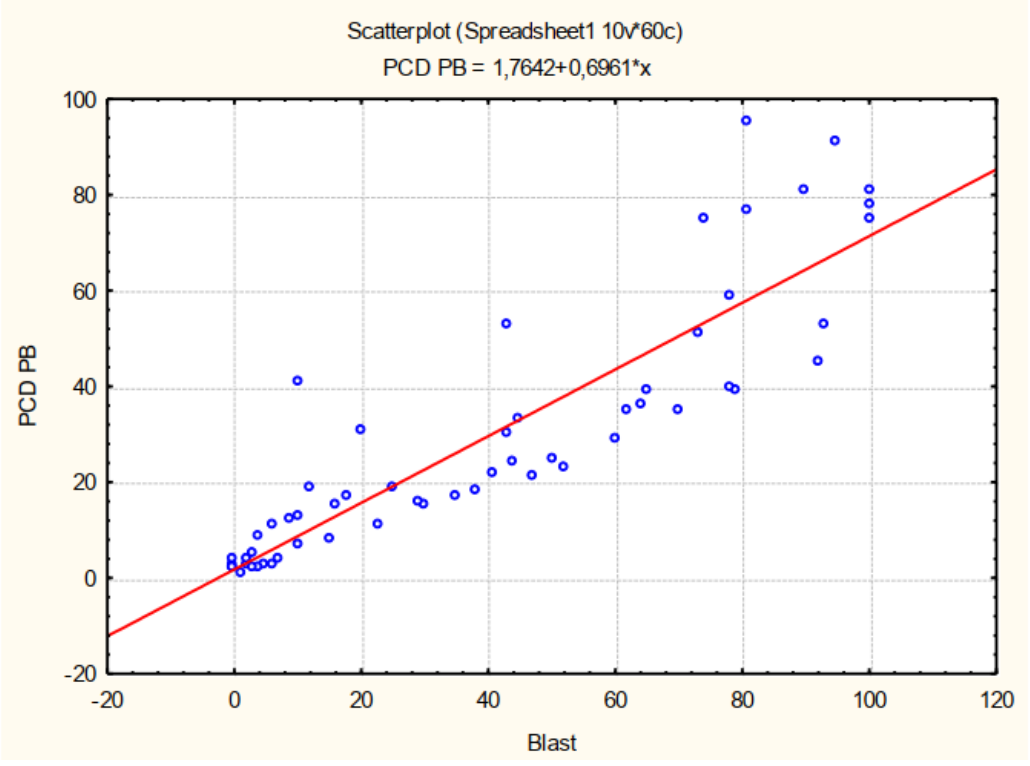

Figure 3: Linear correlation between the level of blasts in the peripheral blood and the level of PCD in the peripheral blood of patients with ALL (r=0.890).

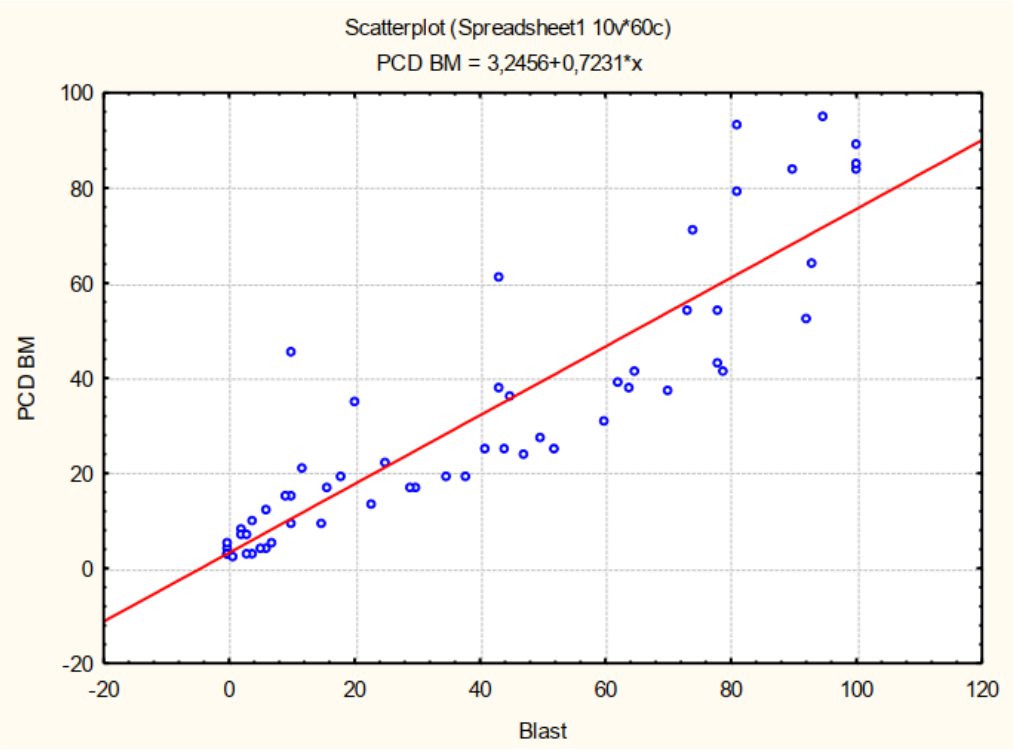

Figure 4: Linear correlation between the level of blasts in the peripheral blood and the level of PCD in the bone marrow of patients with ALL (r=0.896).

Regarding the phenomenon of C-anaphase, no such regularity was found: The correlation coefficient between the level of blasts in peripheral blood and the level of C-anaphase in peripheral blood was only r=0.139, and the correlation coefficient between the level of blasts in peripheral blood and the level of C-anaphase in red bone marrow of the brain was r=0.171 (Figures 5 and 6).

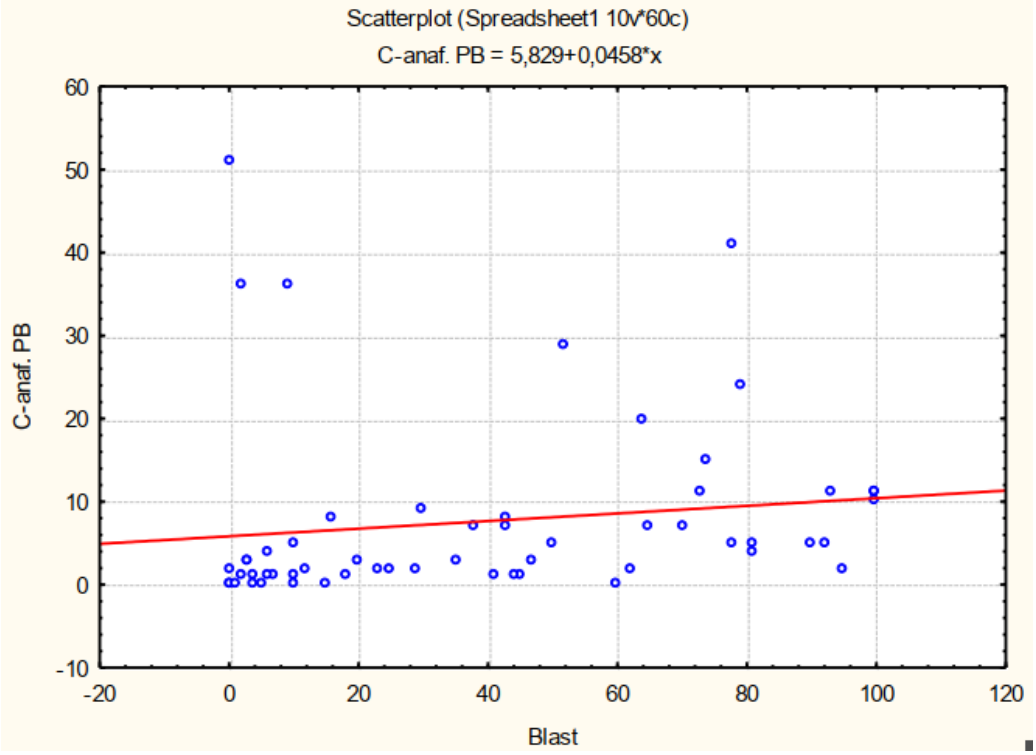

Figure 5: Linear correlation between the level of blasts in the peripheral blood and the level of PCD in the bone marrow of patients with ALL (r=0.896).

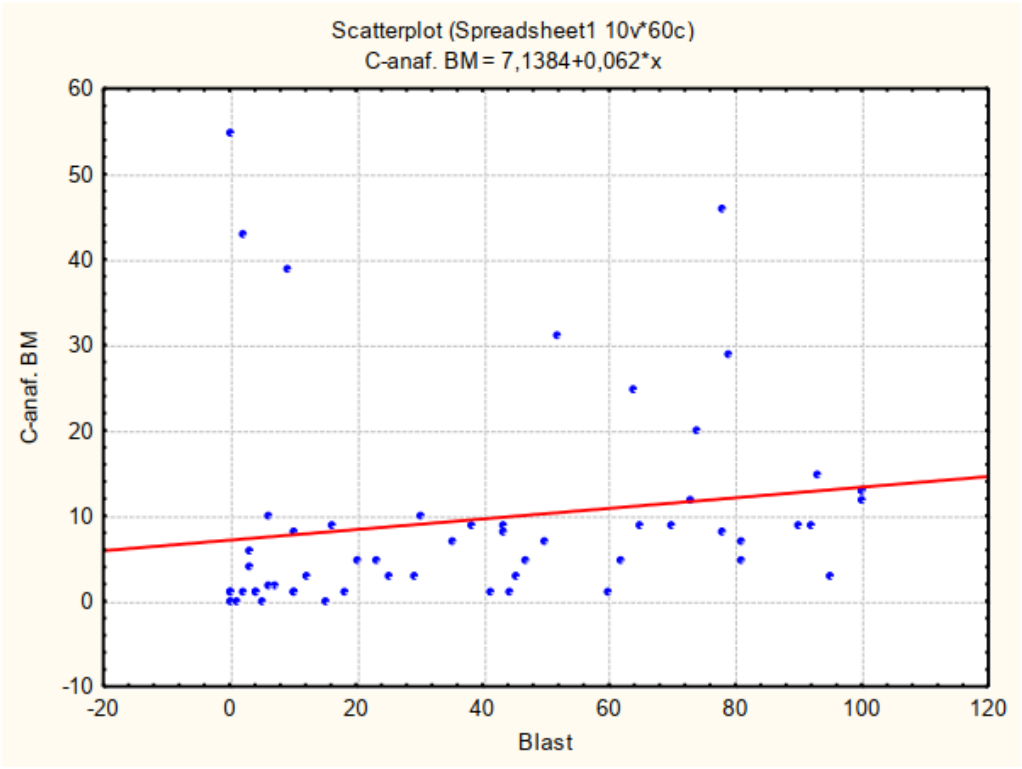

Figure 6: Linear correlation between the level of blasts in the peripheral blood and the level of PCD in the bone marrow of patients with ALL (r=0.896).

DISCUSSION

Similar patterns were obtained in the study of patients with Acute Myeloblastic Leukemia (AML): The correlation coefficient between the level of blasts in Peripheral Blood (PB) and the level of PCD in peripheral blood was r=0.987, and between the level of blasts in peripheral blood and the level of PCD in red Bone Marrow (BM) was r=0.986. Regarding C-anaphase for patients with AML, no relationship with the level of blasts was found: the correlation coefficient between the level of blasts in PB and the level of C-anaphase in PB was r=0.059. These results allow us to state that the phenomenon of PCD is more inherent in blast cells in acute leukemia's than in normal blood cells, the phenomena of PCD and C-anaphase have a different nature and play different roles in the pathogenesis of acute leukemia's. Aneuploid and polyploidy cell clones were found when chromosomal preparations of patients with ALL and AML were examined. The relationship between the level of aneuploid and polyploidy clones in peripheral blood and the levels of PCD and C-anaphase in patients with acute leukemia was investigated. In patients with ALL, it was found that there is a high positive correlation between the level of PCD in peripheral blood and the level of aneuploid clones in peripheral blood: r=0.832. Similarly, a high level of positive correlation was obtained regarding the level of PCD in peripheral blood and the level of polyploid clones in peripheral blood in patients with ALL: r=0.955. Regarding C-anaphase, no such relationship was found: the correlation coefficient between the levels of C-anaphase in PB and the levels of aneuploid clones was only r=0.127; and regarding the level of polyploid clones, r=0.051. The obtained data allow us to state that the phenomenon of PCD is one of the reasons for the instability of the genome of blast cells in patients with acute leukemia-one of the reasons for the formation of aneuploid and polyploid clones among blast cells in the peripheral blood of patients with acute leukemia (Table 2) (Figures 7 and 8).

Type of leukemia	PCD, C-anaphase	Level of aneuploid clones	Level of polyploid clones
ALL	PCD PB	0.832	0.955
	PCD BM	0.851	0.949
	C-anaphase PB	0.127	0.051
	C-anaphase BM	0.143	0.078
AML	PCD PB	0.960	0.909
	C-anaphase PB	0.087	0.044

Table 2: The value of the correlation coefficient (r) between the levels of PCD, C-anaphase and the levels of aneuploid clones and polyploid clones in the peripheral blood of patients with ALL and AML.

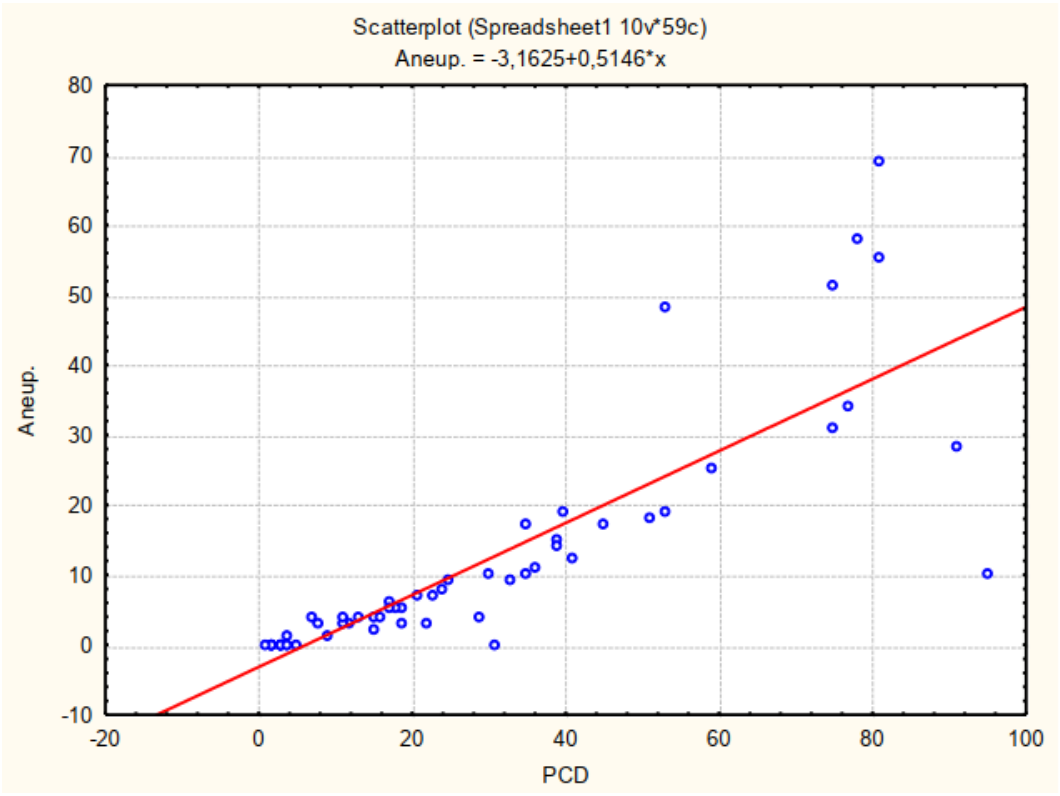

Figure 7: Linear correlation between the frequency of PCD in the peripheral blood cells of patients with ALL and the frequency of aneuploid cells in the peripheral blood (r=0.832)

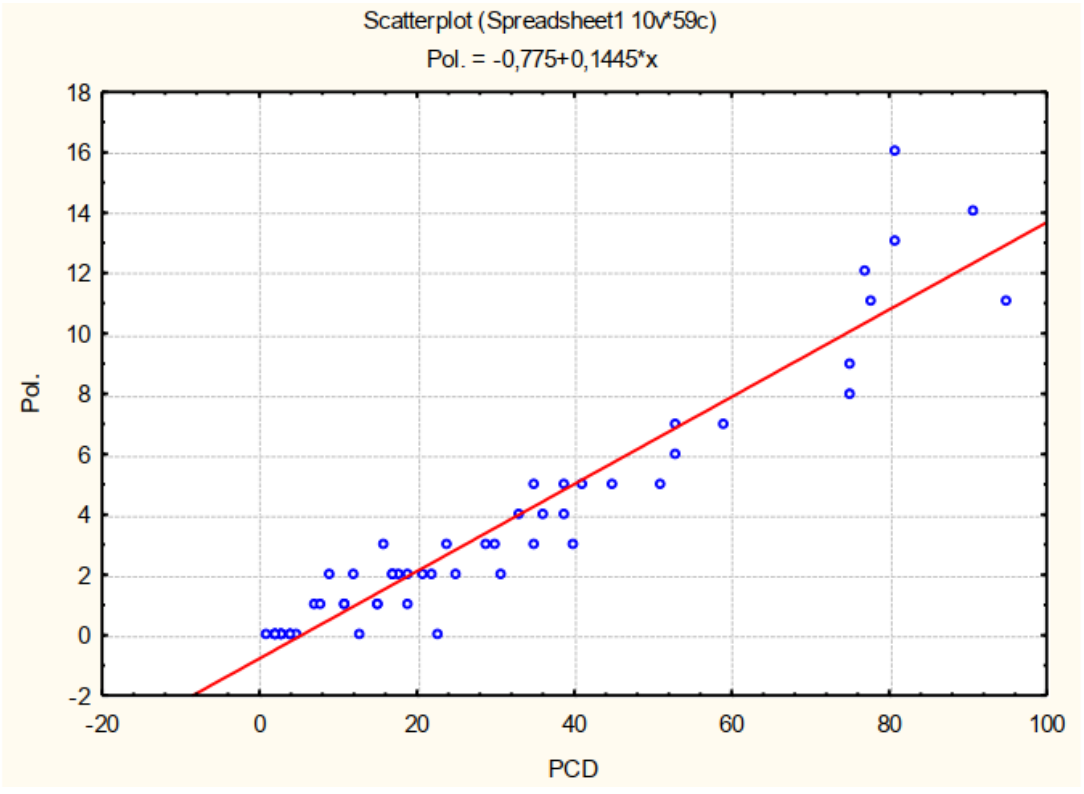

Figure 8: Linear correlation between the frequency of PCD in the peripheral blood cells of patients with ALL and the frequency of polyploid cells in the peripheral blood (r=0.955).

CONCLUSION

The phenomena of PCD and C-anaphase can be used as additional diagnostic criteria of ALL and AML. The phenomenon of PCD is to a greater extent inherent in blast cells than in normal healthy cells in patients with ALL and AML. The phenomena of PCD and C-anaphase can be used as an additional criterion of remission of ALL. The phenomenon of PCD is one of the causes of the instability of the genome of blast cells in patients with ALL and AML-one of the reasons for the occurrence of aneuploid and polyploid clones of blast cells in the peripheral blood of patients with ALL and AML.

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