INDIVIDUAL VARIATIONS OF HEMATOLOGICAL PARAMETERS IN PATIENTS WITH ACUTE LEUKEMIA UNDERGOING THERAPY

Maria DUICU[1] , Mihaela FERICEAN[1], Olga-Alina RADA[1]
Banat's University of Agricultural Sciences and Veterinary Medicine „King Michael I of România", Aradului St. 119, Timişoara 300645, România
radaolga2005@gmail.com

Abstract. *Acute leukaemia represents uncontrolled malign, immature cell proliferations (called blasts) of the hematopoietic system. As opposed to chronic leukaemia, acute leukaemia occurs in a few weeks and determines the precocious occurrence of symptoms, severe in some situations, which renders its diagnosis and treatment extremely important. The diagnosis of acute leukaemia is established based on a blood exam: the complete blood count (CBC), the peripheral blood smear and the red marrow biopsy, highlighting leucocytes, leukemic blasts and thrombocytopenia; usually, anaemia and a haematocrit decrease are registered. It is worrying that the number of leukaemia cases has grown widely during the last years and it is increasingly harder to detect the causes of these genetic changes at cellular level. The purpose of the present study was to capture and highlight the importance of the changes that occurred in the examination of peripheral blood smears and of the automatic complete blood counts, before and after the intervention of the chemotherapy treatment, respectively in the high precision diagnosis of acute leukemias. Patients were monitored during the chemotherapy treatment, with 23 complete blood counts and peripheral blood smears being performed. The analysis and processing of complete blood counts was done following the changes that intensive chemotherapy induces at the level of haematological parameters and on the morphology of blood cells. It has been observed that depending on the individual and the time of diagnosis of acute leukemia, there are wide variations in blood parameters. The response to chemotherapy treatment is also variable over time. Chemotherapy caused the sudden decrease in the number of leukocytes and the complete destruction of leukemic blasts. The investigation of peripheral blood smears supported the results recorded in the processing of automatic complete blood counts for all patients. If the presence of leukemic blasts associated with leukocytosis or leukopenia was detected before chemotherapy, the chemotherapy treatment initially destroyed the leukemic blasts, and then they reappeared on the blood smears. The result indicates the need to consolidate the remission obtained following the first chemotherapy treatment by continuing the treatment until the complete release of the haematogenous bone marrow from the cancer cells, and by resuming the normal haematopoiesis of blood cells.*

Keywords*: acute leukemia, blood counts, blood smears, chemotherapy*

INTRODUCTION

Acute leukemia is a heterogeneous group of clonal neoplastic diseases of undifferentiated or partially differentiated stem cells, characterized by stopping the differentiation and maturation of these cells, associated or not with their passage into the peripheral blood. In the absence of differentiation, the accumulation of these cells gradually leads to the invasion of the bone marrow as well as to the invasion of other vital organs, such as the liver, spleen, lymph nodes, central nervous system, reproductive organs, etc., which constitute the clinical substrate of the disease.

In order to establish the therapeutic behavior and the prognosis, the classification of patients into one of the acute leukemia types (myeloblastic or lymphoblastic) is decisive. To this end, the data from two major world bodies, which deal with these diseases and which have established the exact criteria for classification in a particular type of disease, is corroborated - the FAB-French-American-British classification (BAIN et al., 2010; KINNEY AND LUKENS, 1999, ZINI et al., 2010), which is largely descriptive, and the WHO classification (World Health Organization) issued in 2001 and renewed in 2008, which includes, in addition to

morphological criteria and cytogenetic data, molecular genetics, immunophenotypics and clinical information, making up a true diagnosis algorithm (MUNTEANU et al., 1999; VARDIMAN, J.W., 2009; FEY, M. and BUSKE, C., 2013).

The common treatment of acute leukemia includes chemotherapy, cytostatic drugs, medication that has the ability to destroy tumor cells (https://www.leukemianet.org/content/e77/e4342/e4343/e4417/infoboxContent4973/Pat_Manual_ALL_romanian.pdf.)

Chemotherapy can be intensive (induction, consolidation and maintenance) and non-intensive in elderly patients and with other associated illnesses (https://www.esmo.org/content/download/67393/1215737/file/ESMO-ACF-Leucemia-Acuta-Mieloida-Ghid-Pentru-Pacienti.pdf). Induction chemotherapy can use a single drug administered for 7 days in a row or a dose every three days during the first week. Following this treatment, the hematogenous marrow is expected to become free of any tumor cell. The administration of the induction treatment is done with the continuous monitoring of side effects (anemia, thrombocytopenia, leukocytosis or, less frequently, leukopenia).

It takes another 7-14 days for the hematogenous bone marrow to produce normal blood cells and for the patient to go into remission (https://www.uptodate.com/contents/acute-myeloid-leukemia-aml-treatment-in-adults-beyond-the-basics). If the complete blood count, the peripheral blood smear and the bone marrow aspiration do not indicate the presence of leukemic blasts, then the patient undergoes consolidation chemotherapy, which aims to prevent the relapse and return of the disease in the near future.

MATERIAL AND METHODS

The experimental study involved the monitoring of three patients who presented themselves at the specialist consultation and who, following the complete blood count, presented pathological changes or suspicion of leukemia.

During the monitoring period (13 days for the first patient, 63 days for the second patient and 34 days for the third patient), 23 complete blood counts, respectively peripheral blood smears, were done. The analysis and processing of complete blood counts was done following the changes that intensive chemotherapy induces at the level of hematological parameters and on the morphology of the blood cells.

The study of blast cells was done from blood harvested by venipuncture in vacutainers for the blood count, with EDTA anticoagulant, without prior centrifugation or by puncture of the finger pulp (peripheral blood). The automatic complete blood counts were done with the automatic hematology analyzer-Sysmex XN-1000. The device performs complete blood counts, measuring a series of hematological parameters from the entire venous blood drawn on the K2EDTA as an anticoagulant, in a ratio of 9:1. The samples are analyzed within a maximum of 2 hours after harvesting, without being stored in the refrigerator (SR EN ISO 15189, 2013). Following the automatic complete blood count, blood smears were mandatory for all patients to confirm or deny the diagnosis. Peripheral blood smear is a test that aims to establish, first, the morphology of the blood cells, then confirm their belonging to a certain type of leukocytes by manually performing the counting according to the smear counting technique (300 elements are counted, then the percentage that each type of leukocytes represents from their total number using mathematical formulas is calculated).

RESULTS AND DISCUSSIONS

1. Analysis and processing of automatic complete blood counts

The complete blood count provides direct signs for the diagnosis of leukemia (presence of leukemic blasts) (RADA et al., 2017a, PĂCURAR, 2013) and indirect signs of bone marrow failure (anemia, neutropenia, thrombocytopenia) (Ostan et al., 2017). The evolution of the hematological parameters during the monitoring of the hospitalized patients is shown in tables 1, 2 and 3 and figures 1-6.

The analysis and processing of the automatic complete blood counts of patient no. 1 shows, before the chemotherapy treatment, a very large number of leukocytes, with a value of 166.51/*103/μL, that is 16.65 times higher than the maximum limit of the biological reference range (4-10/*103/μL). The presence of 78% leukemic blasts in all examined cell types is also reported (Table 1, Fig. 1). Erythrocytes were below the minimum limit of the biological reference range (4-5.2/*10³/μL), respectively 2.64/*10³/μL, while the hemoglobin amount was 7.8, namely 65% of the minimum value of the biological reference range, suggesting secondary anemia installed. The platelets had a value of 40/*10³/μL, that is 26.22% of the minimum value of the biological reference range, the thrombocytopenia being associated with leukemia. Because of the decrease in the number of all blood cell types, the hematocrit had a lower value as well, namely 62% of the minimum value of the biological reference interval (24.8%).

Subsequent complete blood counts done after the chemotherapy treatment (after 5 days, 6 days, 7 days, 8 days, and 13 days) show a drastic decrease in the number of leukocytes, which is maintained almost constant throughout the monitoring period (Fig. 2). The number of red blood cells, the amount of hemoglobin and the hematocrit did not show significant variations after the chemotherapy treatment, but they remained below the minimum limit of the biological reference range. The number of platelets decreased sharply, with an average value after chemotherapy of 2.6±1.81/*10³/μL, namely 1.73% of the minimum limit of the biological reference range, indicating an extremely severe thrombocytopenia (Fig. 2).

Table 1.

Evolution of hematological parameters in patient no. 1, during the entire monitoring period

Patient no. 1 Age of patient (years): 39 Sex of patient (m/f): f	Blood count						Average	Biological reference range/ Measurement unit*
	1	2	3	4	5	6		
Monitoring (days)	0	5	6	7	8	13		
Leukocytes (*10³/μL)	166,51	1,61	2,96	1,15	0,43	0,63	28,88±67,42	4-10 / *10³/ μL
Erythrocytes (*10³/μL)	2,64	3,39	2,95	3,11	2,49	2,17	2,79±0,44	4-5,2 / *10³/μL
Hemoglobin (g/dL)	7,8	10	8,7	9,2	7,4	6	8,18±1,42	12-15 / g/dL
Hematocrit (%)	24,8	30	26,4	27,6	21,9	17,9	24,76±4,32	40-50 / %
Platelets (*10³/μL)	40	5	2	4	1	1	8,83±15,35	150-410 / *10³/μL
Percentage of blasts in the peripheral blood (%)	78	1	0	0	0	0	39,5±54,44	%

The colored values are outside the biological reference range

*BAIN et al., Dacie and Lewis Practical Hematology, 12th edition, London, UK, 2012.

The analysis and processing of the automatic complete blood counts of patient no. 2, reveal a hematological picture different from the previous case, suggesting the individual response to the proposed therapy. Chemotherapy was performed after one week of monitoring. Prior to chemotherapy, leukocyte values and the presence of leukemic blasts justify the diagnosis of acute leukemia: leukocytes recorded 81.85/*103/μL, 68.13/*103/μL, respectively

41.11/*103/μL, well above normal values, and leukemic blasts were present in 87%, respectively 80% of the total blood cells (Table 2, Fig. 3).

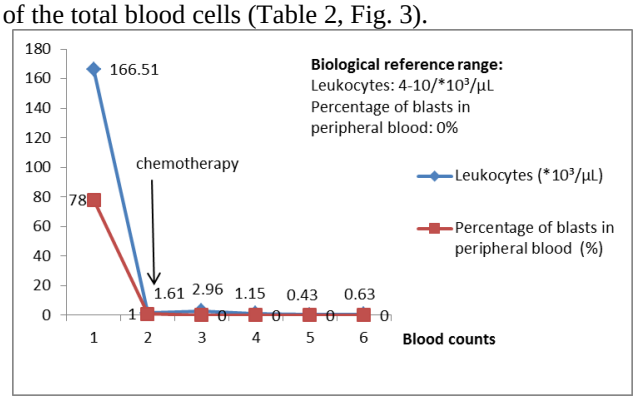
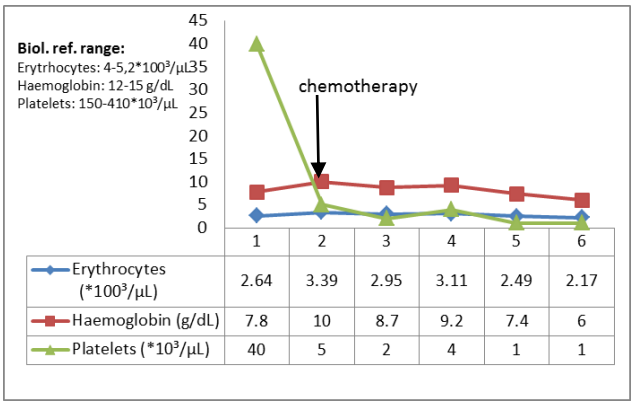


Figure 1. Variation of the leukocytes and leukemic blasts number before and after chemotherapy treatment in patient no.1



	1	2	3	4	5	6
Erythrocytes (*100³/μL)	2.64	3.39	2.95	3.11	2.49	2.17
Haemoglobin (g/dL)	7.8	10	8.7	9.2	7.4	6
Platelets (*10³/μL)	40	5	2	4	1	1

Figure 2. Variation of erythrocytes number, hemoglobin and hematocrit amount before and after chemotherapy treatment in patient no.1

Erythrocytes and hemoglobin had values below the minimum biological reference range, suggesting the installation of secondary and progressive anemia. Also, thrombocytopenia was suggested by the small number of platelets (68/*10³/μL, 54/*10³/μL and 43/*10³/μL) compared to the biological reference range (150-410/*10³/μL) (Fig. 4).

After chemotherapy, the number of leukocytes decreased, registering very low values (1.21/*10³/μL; 0.47/*10³/μL, respectively 0.54/*10³/μL) until the 21st day of monitoring. At 28 days of monitoring, the number of leukocytes fell within normal limits (4.91/*10³/μL). Later, on day 63 of monitoring there was an increase up to 15.22/*10³/μL (Table 2, Fig. 3). The percentage of leukemic blasts has an uneven evolution, without correlating with the number of leukocytes. If, initially after chemotherapy, the percentage decreases, then on day 28 of monitoring, 18% of leukemic blasts are registered in the total blood cells.

The number of erythrocytes and the amount of hemoglobin did not vary significantly compared to the values prior to the chemotherapy treatment, suggesting the maintenance of anemia. The average number of erythrocytes recorded after chemotherapy was 2.54±0.5/*100³/μL (63.5% of the minimum biological reference range), while the mean value of hemoglobin was 7.8±1,43/g/dL (65% of the minimum value of the biological reference

range). The number of platelets showed the greatest variations after chemotherapy. If initially the number of platelets decreases significantly (due to the suppressive effect of the drugs on the bone marrow platelet precursors), on the 28th day of monitoring there is a significant increase, the value approaching the minimum value of the biological reference range (127/*10³/μL) (Table 2, Fig. 4).

Table 2.

Evolution of hematological parameters in patient no. 2, during the entire monitoring period

Patient no. 2 Age of patient (years): 55 Sex of patient (m/f): f	Blood count								Average	Biological reference range/ Measurement unit*
	1	2	3	4	5	6	7	8		
Monitoring (days)	0	2	5	9	14	21	28	63		
Leukocytes (*10³/μL)	81,85	68,13	41,11	1,21	0,47	0,54	4,91	15,22	26,68±32,93	4-10 / *10³/ μL
Erythrocytes (*100³/μL)	2,30	2,14	2,02	2	2,13	2,58	3,26	2,75	2,39±0,43	4-5,2 / *100³/μL
Hemoglobin (g/dL)	7,2	7,3	7,3	6,3	6,6	7,6	9,6	8,9	7,6±1,11	12-15 / g/dL
Hematocrit (%)	21,8	20	19,3	18,4	19,3	22,5	29	26,4	22,08±3,78	40-50 / %
Platelets (*10³/μL)	68	54	43	28	7	2	127	112	55,12±45,65	150-410 / *10³/μL
Percentage of blasts in the peripheral blood (%)	87	80	0	6	0	1,9	18	0	38,58±41,50	%

The colored values are outside the biological reference range

*BAIN et al., Dacie and Lewis Practical Hematology, 12th edition, London, UK, 2012.

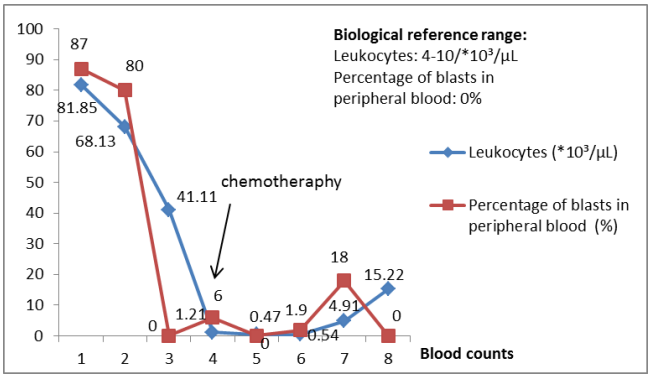


Figure 3. Variation of leukocytes and leukemic blasts number before andafter chemotherapy treatment in patient no. 2

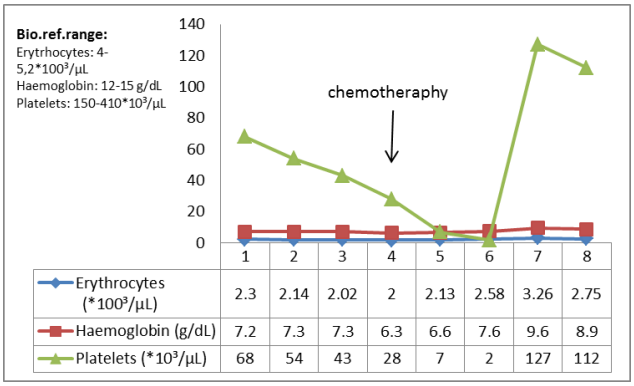


Figure 4. Variation of erythrocytes number, hemoglobin and hematocrit amount before and after chemotherapy treatment in patient no. 2

The analysis and processing of automatic complete blood counts of patient no. 3 reveal a particular situation; the suspicion of acute leukemia was given by the presence of leukemic blasts, not by the number of leukocytes. At the beginning of the monitoring, before establishing the therapeutic behavior, the complete blood count shows leukopenia, that is a small number of leukocytes (2.98/*10^3/μL), a very rare case, because it is known that the clinical picture for acute leukemias implies the presence of leukemia blasts and a very high number of leukocytes (leukocytosis) compared to the biological reference range. Leukopenia was maintained throughout the first week of monitoring, accompanied by the presence in the blood of leukemia blasts (Table 3 and Fig. 5).

Similar to the other cases analyzed, the erythrocytes were in small number, below the minimum value of the biological reference range, namely 2.44/*100^3/μL (61% of the normal minimum) and the hemoglobin amount was 7.7 g/dL, representing 64.16% of the minimum value of the biological reference range. Also, the number of platelets was very low, only 5/*10^3/ μL, namely 3.33% of the minimum value of the biological reference range. These values reveal the anemia and secondary thrombocytopenia associated with leukocytopenia in this clinical picture. Due to the very low values of the number of blood cells, the hematocrit recorded a value of 22.5%, only 56.25% of the minimum value of the biological reference range (Fig. 6.). After the chemotherapy treatment, the number of leukocytes decreases further, reaching an average value of 0.66±0.2/*10^3/μL during the first post-chemotherapy week, that is only 16.5% of the minimum value of the biological interval of reference. In the second week after chemotherapy, the number of leukocytes returns to normal biological parameters (5.18/*10^3/μL, respectively 9.66/*10^3/μL), and afterwards, 18 days after the chemotherapy treatment, it shows a new drop to a value of 0.53/*10^3/μL. After chemotherapy, the presence of leukemic blasts is not detected until two weeks later, when unexplainably, their presence in the peripheral blood is detected again. The number of erythrocytes and the amount of hemoglobin have an almost linear evolution, very similar to the values from the beginning of the monitoring. The number of platelets continues to be very low even after the chemotherapy treatment, except for the last week of monitoring, when the number of platelets shows an increase, but it fails to reach the minimum value of the biological reference range. Consequently, anemia and thrombocytopenia are maintained post-chemotherapy (Fig. 6).

Table 3.

Evolution of hematological parameters in patient no. 3, during the entire monitoring period

Patient no. 3 Age of patient (years): 61 Sex of patient (m/f): m	Blood count									Average	Biological reference range/ Measurement unit*
	1	2	3	4	5	6	7	8	9		
Monitoring (days)	0	3	7	16	22	24	28	30	34		
Leukocytes (*10^3/μL)	2,98	1,79	1,59	0,40	0,80	0,78	5,18	9,66	0,53	2,89±3,13	4-10 / *10^3/ μL
Erythrocytes (*100^3/μL)	2,44	3,05	2,82	2,75	3,25	3,0	2,93	3,32	2,60	2,94±0,28	4-5,2 / *100^3/μL
Hemoglobin (g/dL)	7,7	9,4	8,8	8,2	9,6	8,9	8,4	9,4	7,5	8,8±0,66	12-15 / g/dL
Hematocrit (%)	22,5	28	26,4	24,9	28,6	26,3	24,6	27,6	22,8	26,11±2,03	40-50 / %
Platelets (*10^3/μL)	5	4	8	2	6	2	11	27	14	8,12±8,20	150-410 / *10^3/μL
Percentage of blasts in the peripheral blood (%)	8	2	2	0	0	0	0	3	0	3,75±2,87	%

The coloured values are outside the biological reference range

*BAIN et al., Dacie and Lewis Practical Hematology, 12th edition, London, UK, 2012.

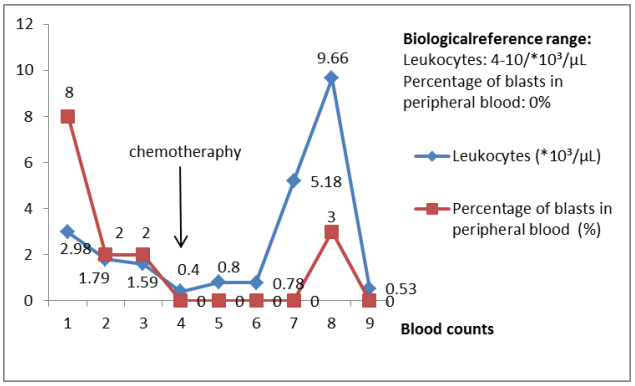
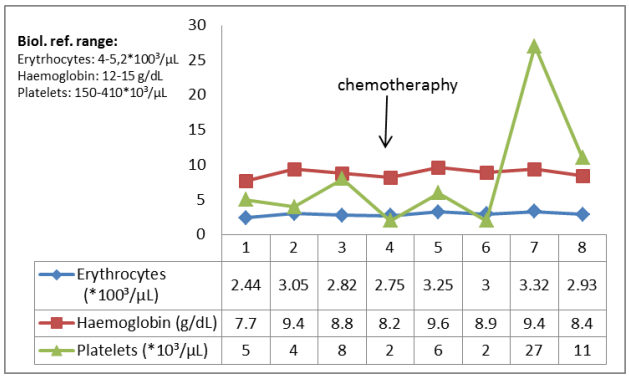


Figure 5. Variation of the leukocytes and leukemic blasts number before and after chemotherapy treatment in patient no.3



	1	2	3	4	5	6	7	8
Erythrocytes (*100³/µL)	2.44	3.05	2.82	2.75	3.25	3	3.32	2.93
Haemoglobin (g/dL)	7.7	9.4	8.8	8.2	9.6	8.9	9.4	8.4
Platelets (*10³/µL)	5	4	8	2	6	2	27	11

Figure 6. Variation of erythrocytes number, hemoglobin and hematocrit amount before and after chemotherapy treatment in patient no. 3

2. Investigating peripheral blood smears

The examination of the peripheral blood smears under the microscope (with lens 20) for the first patient before chemotherapy treatment reveals the existence of immature white line cells (blasts) in a very high percentage compared to the total blood cells present, which normally should not be found in a healthy patient. In addition, erythrocyte hypochromia (anemia) is also observed (Fig. 7). Leukemic blasts are larger in size than a normal cell, the nucleus/cytoplasm ratio is big, the cytoplasm is fine and mostly has vacuoles, the nucleus has visible nucleoli. All these observations confirm the data obtained by processing the automatic complete blood counts. After chemotherapy, the drastic decrease of white blood cells (leukopenia) is observed, with anemia maintaining (erythrocytes are strongly hypochromic) (fig. 8).

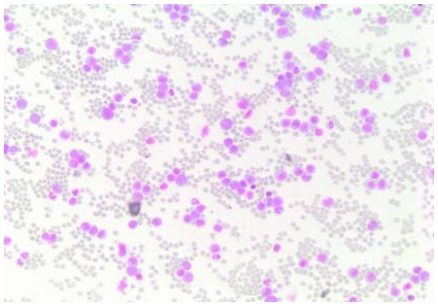


Figure 7. Very large number of white cells (leukocytosis) with increased percentage of peripheral blasts, before chemotherapy (x20, original)

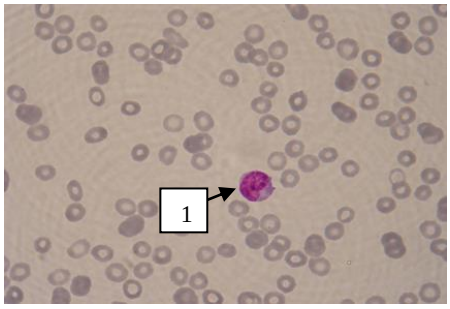


Figure 8. Severe leukopenia, after chemotherapy; monocyte with pathological aspect (1); hypochromic erythrocytes (x100, original)

The examination of peripheral blood smears in patient no. 2 before chemotherapy, reveals the presence of large leukemic blasts (leukocytosis) accompanied by normoblasts (erythroblasts), immature erythrocytes that passed into the peripheral blood before maturing, probably because of the anemia associated with acute leukemia. The blasts have a monocitoid appearance with large nuclei, visible nucleoli and vacuolated cytoplasm (fig. 9). Erythrocytes are hypochromic confirming the anemia associated with acute leukemia. After the chemotherapy treatment, the total number of white blood cells is observed, but the presence of leukemic blasts is maintained. The blood smear test was done on the 28th day of monitoring when the automatic complete blood count showed normal leukocyte levels, but the presence of leukemic blasts was detected, suggesting that the response to the first chemotherapy-induced remission treatment is not favorable (fig. 10).

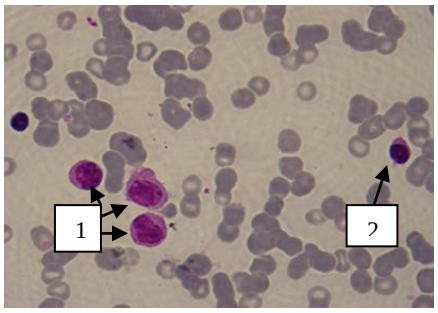


Figure 9. Blasts with monocitoid aspect, big nucleus with visible nucleoli and vacuolated cytoplasm (1); normoblasts present (2), before chemotherapy (x100, original)

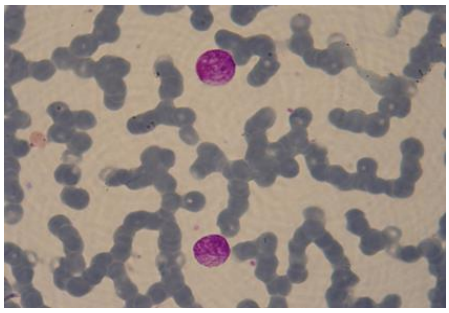


Figure 10. Pathological promyelocyte (up), myelocyte (down); agglomerated erythrocytes, after chemotherapy (x100, original)

The examination of blood smears before chemotherapy in patient no. 3, reveals leukopenia (smaller than normal number of leukocytes), but leukemic blasts are present. They have myeloid appearance, large nucleo/cytoplasmic ratio, eucromatinic nucleus with visible nucleoli and intense basophilic cytoplasm with few azurophilic granules (fig. 11). Erythrocytes are hypochromic, confirming the anemia revealed by reading the automatic complete blood counts.

After the initiation of the chemotherapy treatment to induce remission, leukopenia deepens; hypogranular segmented cells with rare granulations and/or the absence of intracytoplasmic granulations associated with acute myeloblastic leukemia are present (Fig. 12). Erythrocytes are hypochromic (anemia) and have the appearance of a roll. This aspect is maintained throughout the monitoring period, in accordance with the results of the automatic complete blood counts.

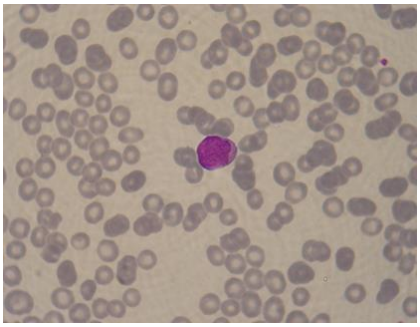


Figure 11. Blast with myeloid aspect, large nucleo-cytoplasmatic ratio, euchromatinic nucleus with visible nucleoli, basophilic cytoplasm, before chemotherapy (x100, original)

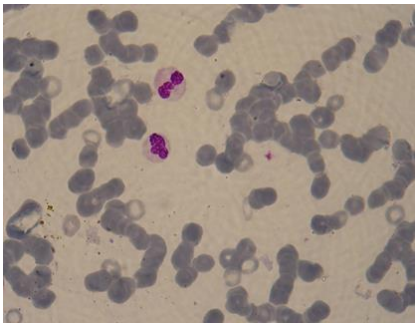


Figure 12. Pathological hypogranular segmented cells, after chemotherapy (x100, original)

CONCLUSIONS

1. The diagnosis of acute leukemia is based on the examination of the blood: the complete blood count, the peripheral blood smear and the biopsy of the hematogenous bone marrow, with the detection of leukocytes, the presence of leukemic blasts and thrombocytopenia; usually anemia and decreased hematocrit are recorded.

2. Depending on the individual and the time of diagnosis of acute leukemia, there are wide variations in blood parameters. The response to chemotherapy treatment is also variable over time.

3. Chemotherapy determines the abrupt decrease in the number of leukocytes and the complete destruction of leukemic blasts.

- patient no. 1, monitored for 13 days: after the administration of the chemotherapy treatment, leukopenia was installed and the number of leukemic blasts decreased to zero;

- patient no. 2, monitored for 62 days: post-chemotherapy leukopenia was maintained for 21 days; at 28 days, the number of leukocytes had normal values, and at 63 days leukocytosis occurred. Leukemic blasts decreased to zero after chemotherapy, but were present again in the peripheral blood at 28 days;

- patient no. 3, monitored for 34 days: the administration of the chemotherapy treatment determines a different evolution compared to the other cases. The diagnosis of acute leukemia was established because of the presence of leukemic blasts associated with leukopenia. One week after the chemotherapy treatment, leukopenia increased, and after another 7 days the leukocytes showed normal values. Later, leukopenia was present again. Leukemic blasts disappear after chemotherapy treatment, until 14 days when they reappear in the peripheral blood.

4. The investigation of peripheral blood smears supported the results recorded in the processing of automatic complete blood counts for all patients. Prior to chemotherapy, the

presence of leukemic blasts, associated with leukocytosis (patient 1 and 2) or leukopenia (patient 3), was detected. The chemotherapy treatment initially destroyed the leukemic blasts, and then they reappear on the blood smears. Thus, we can say that it is necessary to strengthen the remission obtained with the first chemotherapy treatment, by continuing the treatment until the complete release of the hematogenous bone marrow from these cancer cells and the resumption of normal hematopoiesis of the blood cells.

BIBLIOGRAPHY

BAIN, J. BARBARA, DAVID, M.C., BRIDGET, S., 2010 - Bone Marrow Pathology, Wilkins 4th Edition, Willy-Blacwell, Oxford, UK.

BAIN J. BARBARA, BATES, IMELDA, LAFFAN, M.A., LEWIS, S.M., 2012 - Dacie and Lewis- Practical hematology 12th Edition, Curchill Livingstone, Edinburgh, London, Melbourne and New York.

FEY, M.F., BUSKE, C., 2013 - Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology, 24 (6): p.138-143.

KINNEY, M.C., LUKENS, J.N., 1999 - Wintrobe's Clinical Hematology,10th Edition.

MUNTEANU, N., RADU, P., COLITA, D., 1999 - Tratat de medicina internă - Hematologie Clinică, partea a-II-a, Editura Medicală, Bucureşti.

PĂCURAR, R., 2013 - Identificarea blaştilor din sângele periferic cu ajutorul analizorului Sysmex XT-2000i-Premise Clinice, Al 4-lea Simpozion Top Diagnostics „Excelenţa în hematologie, Bucureşti.

PHILLIPS, G.L., REECE, D.E., SHEPHERD, J.D., BARNETT, M.J., BROWN, R.A., FREI-LAHR, D.A., KLINGEMANN, H.G., BOLWELL, B.J., SPINELLI, J.J., HERZIG, R.H., 1991 - High-dose cytarabine and daunorubicin induction and postremission chemotherapy for the treatment of acute myelogenous leukemia in adults, Blood, 77(7):1429.

RADA, O.A, MĂRAN, C. L., OSTAN, M., 2017 - a-Morphological and chemical changes in blood cells in acute leukaemia in humans Note 1. Analysis of blood count in patients with suspected acute leukaemia, Research Journal of Agricultural Science, 49 (3), p. 81-86, ISSN 2066-184.

OSTAN, M., SURDILĂ, A.M., MĂRAN, C.L., SAVICI, J., RADA, O.A., 2017 - Changes of blood cells in thrombocytopenia in humans, Research Journal of Agricultural Science, 49 (3), p. 52.

VARDIMAN, J.W., THIELE, J., ARBER, D.A., BRUNNING, R.D., BOROWITZ, M.J., PORWIT, A., HARRIS, N.L., LE BEAU, M.M., HELLSTROM-LINDBERG, E., TEFERI, A., BLOOMFIELD, C.D., 2009 - The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes, Blood, 114 (5):937-51.

ZINI G., BAIN, B., BETTELHEIM, P., CORTEZ, J., D'ONOFRIO, G., FABER, E., HAFERLACH, T., KACIRKOVA, P., LEWANDOWSKI, K., MATUTES, E., 2010 - European consensus report on blood cell identification: terminology utilized and morphological diagnosis concordance among 28 experts from 17 countries within the European LeukemiaNet network WP10, on behalf of the ELN Morphology Faculty, BJH 151, 359-364.

SR EN ISO 15189, 2013 - Regulament specific de acreditare în domeniul acreditării laboratoarelor medicale, Asociația de Acreditare din România.

https://www.leukemianet.org/content/e77/e4342/e4343/e4417/infoboxContent4973/Pat_Manual_ALL_romanian.pdf (accessed on October 14, 2019).

https://www.esmo.org/content/download/67393/1215737/file/ESMO-ACF-Leucemia-Acuta-Mieloida-Ghid-Pentru-Pacienti.pdf (accessed on October 14, 2019).

https://www.uptodate.com/contents/acute-myeloid-leukemia-aml-treatment-in-adults-beyond-the-basics (accessed on October 14, 2019).