**Neutrophil, Monocyte, Basophil and Eosinophil Evaluation of Acute Myeloid Leukemia Patients Within 4 Growth Levels**

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**Abstract:**

 Evaluation of sixty patients pre and post 3 and 7 protocol regimen compared with 60 apparently healthy volunteer dispersed on 4 age groups (0-15, 16-40, 41-65, 65 and above years). The results show low neutrophil count before treatment in all age groups and shows statistical differences when compared with the post treatment samples that shows elevation in count to near from control values. Evaluations of monocyte and basophil shows higher than control and post treatment count which give arise to the statistical differences to appear between treatment groups. Comparison between age groups in neutrophil and monocyte shows statistical differences when compared between age groups. Eosinophil evaluation shows no statistical differences when compared between treatment group and age group. All statistical comparisons done be ANOVA on P≤0.5.

**Key words:** Basophil, Neutrophil, Eosinophil, Monocyte, Acute myeloid leukemia.

**Introduction:**

Acute Myeloid Leukemia

Blood malignancy influences WBCs, PLTs and RBCs. An individual with AML creates anomalous quantities of these cells rapidly, giving the name "acute". The WBC count is either upper or under than ordinary count, which are all in blast stage. Since WBCs are a significant piece of battling contaminations, patients regularly have different uncurable diseases. A few patients develop low RBC count and/or PLTs count, yet that is not generally1.

**Signs:**

In AML, certain WBC do not completely develop and cannot work appropriately. Side effects are identified with the strange numbers and capacity of immature WBC. They can incorporate fever, contamination, simple draining or wounding, shortness of breath, or shortcoming. These side effects can likewise be indications of basic sicknesses like influenza. It is not exceptional for an individual back to human services supplier before getting a finding of AML. Most contaminations are simply diseases and not leukemia. What is significant is that an individual comes back to their social insurance supplier for further examination if the side effects they have are not reacting to the endorsed treatment (regularly anti-toxins)2.

Acute myeloid leukemia frequently found when an individual has an un treated disease or draining or wounding and abnormal blood component counts. In these cases further investigations should be done3.

**Diagnostic Methods:**

1. Biopsy from bone marrow to determine the classification of AML. Include cytogenetic testing (karyotype and/or FISH testing), immunophenotyping, molecular testing, and human leukocyte antigen (HLA) typing for potential future bone marrow transplant. Classification helps to guide treatment. There are two classification systems for AML4.
2. World Health Organization order of AML (2016) utilizes hereditary variations from the norm to group classes of it. That framework modify the idea and vision toward AML diagnosis to more than twenty percent of immature cells in BM and gatherings different subtypes of AML dependent on hereditary variations from the norm and forecast*.*

Acute myeloid leukemia (AML) and related neoplasms

The second classification system for AML is FAB grouping (M0 – M7). The FAB (French American British) (2016) order. The FAB framework depends on the percentage of more than thirty percent immature cells in BM to allocate an analysis.

Patients characterized into prognosis hazard gatherings (ideal, moderate and poor) in view of the hereditary variations, that may help decide the best proper treatment.

**Treatment:**

Chemotherapy is perplexing. It is separated into two stages, acceptance stage and solidification (or increase) stage. The objective of acceptance treatment is to instigate an abatement, generally characterized as under 5% blasts in BM. When reduction accomplished, combination treatment prescribed. Medical procedure is not utilized in light of the fact that AML is an infection of the blood, which circles all through the entire body; this implies a viable treatment which must be addressed. Determination of treatment routine reliant on how old patients are and their FAB classification5.

The treatment is intended to crash the strangely working leukemia cells, yet this treatment demolishes numerous solid cells, also. Putting the patient in danger for draining and disease. Which can be dangerous. Furthermore, the chemotherapy prescriptions can cause symptoms, for example, mouth wounds (mucositis), loose bowels, sickness/regurgitating, and male pattern baldness (alopecia)6.

Protocol followed in the treatment of AML:

For patients under 60 years: 3 and 7 protocol (3 days of anthracycline like daunorobicine or doxorubicin and 7 days of cytosine arabinoside. (Stone, *et al*. 2017). Bone marrow transplantation may be chosen also for them depending on their general health status7.

For patients above 60 years: the 3 and 7 combination admitted together or even in a lower intensity than it is for patients under 60 because of their general health status5.

For patients who do not endure the treatment the receive blood and hydroxyurea (to reduce the WBC count to reduce symptoms)6.

**What after Treatment?**

Full remission means blast percentage less than 5% in bone marrow. Also further diagnostic tests should be done to ensure the total remission of the patients and that should be done every month then every 6 months4.

There are three terms which we should understand before proceeding in the literature review defined by American cancer society (2018)8.

* + 1. Remission (complete remission):

No evidence of disease after treatment. (NED).

* + 1. Minimal residual disease: which means zero leukemic cells seen in BM after treatment ends that performed either by normal microscope examination or by flowcytometry or Polymerase chain reaction.
		2. Active disease: presence of leukemic cells during therapy receiving or after therapy completed which called relapse and that reported when blast percentage is above five percent in bone marrow.

**Diagnosis of AML:**

**Count of White Blood Cells:**

Elevated white blood cells count more than one hundred thousand connected to a more risk9.

**Methods:**

 **Experiment design:**

1. **Selection of patients and control group:**

A total of sixty patients presented to national center of hematology and special nursing center with AML symptoms in the period between (01/05/2018 to 20/09/2018). CBC test performed to all of them to ensure the diagnosis.

**Patients Group:** Sixty cases who met the hematological and immunological diagnostic criteria for CBC, ALL, CLL and CML were excluded. Another 60 Peripheral Blood sample collected from the same patients a month after receiving 3 and 7 protocol (3 days of anthracycline and 7 days of cytosine arabinoside) to evaluate the prognosis of each case.

Patients divided into 4 age groups according to growth level 1st 0-15 years, 2nd 16-40 year, 3rd 41-65 year, 4th 66 years and above in a reality of 15 patient for each age group . male to female percentage were 2:1. (Britannica 2019).

 **Control Group:** Sixty non-AML healthy volunteer peripheral blood samples collected in the same age groups and male to female ratio of patients.

1. **Inclusion and exclusion criteria:**

Patients and control group include:

1. Patients who were with AML according to their Complete Blood Count evaluation.
2. Same patients a month after 3 and 7 protocol.

Exclusions:

1. Patients received treatment before we collect the pretreatment sample.
2. Patients with ALL, CLL and CML.
3. Patients who passed before post treatment sample collecting.
4. **Sample preparation method:**

Two ml of PB collected in EDTA tube to perform CBC count test.

**Complete Blood Count Test:**

The Sysmex® (2019)10 technique precisely tallies.this test performed at Baquba teaching hospital/ Diyala / Iraq.

Sysmex Analyzer is a quantitative, mechanized hematology analyzers estimates these parameters in entire blood:

HB, HCT, WBC, MCV, RBC, MCH, MCHC, Platelet, MPV, Neutrophil, Lymphocyte, Basophil, Eosinophil, Monocyte.

The techniques used to infer CBC parameters depends on the Sysmex® strategy for tallying and estimating, in mix with a programmed weakening and blending gadget for test preparing utilize three concurrent estimations of individual cell volume (V), high recurrence conductivity (C), and laser light disperse (S). All items depend on the estimations of these three parameters.

**Results and Discussion:**

 Neutrophil level of pre-treatment group shows low level below the normal range of control group or even the international reference value of neutrophil count. Also significant difference appear when compare post treatment group of the same age group. No statistical differences appear between age groups as a whole that reflect that all ages show the same response regarding neutrophil count. Table 1.

 **Table 1. Effect of Treatment and age groups in Neutrophil**

|  |  |  |
| --- | --- | --- |
| Age groups (year) | Mean ± SE of Neutrophil % | ANOVA value |
| Pre-Treatment  | Post-Treatment | Control |
|  1-15 | 1.58 ± 0.21 | 4.25 ± 0.43 | 6.43 ± 0.67 | 1.370 \* |
| 16-40 | 2.08 ± 0.28 | 4.75 ± 0.56 | 4.91 ± 0.42 | 1.261 \* |
| 41-65 | 0.696 ± 0.15 | 2.54 ± 0.74 | 5.94 ± 0.77 | 1.793 \* |
| 66 and above | 1.15 ± 0.19 | 3.12 ± 0.38 | 5.77 ± 0.49 | 1.089 \* |
| LSD value | 0.621 \* | 1.564 \* | 1.727 NS | --- |
| \* (P<0.05). |

The monocyte usually elevated during infections11 even though and in the case of total miscount and elevation in WBC count the 1st, 3rd and 4th age group typify that evaluation in this our study in children age group which pass the other pre-treatment patients in 3rd and 4th age group. While the 2nd age group shows no statistical difference from comparison between pre and post treatment group. Only 1st and 4th age group shows statistical differences. As shown in table 2.

**Table 2. Effect of Treatment and age groups in Monocyte**

|  |  |  |
| --- | --- | --- |
| Age groups (year) | Mean ± SE of Monocyte % | ANOVA value |
| Pre-Treatment  | Post-Treatment | Control |
|  1-15 | 5.67 ± 1.38 | 0.814 ± 0.25 | 0.710 ± 0.10 | 2.322 \* |
| 16-40 | 0.736 ± 0.19 | 0.401 ± 0.09 | 0.592 ± 0.07 | 0.380 NS |
| 41-65 | 2.83 ± 2.00 | 2.40 ± 1.81 | 0.761 ± 0.05 | 4.456 NS |
| 66 and above | 2.50 ± 0.66 | 0.814 ± 0.10 | 0.568 ± 0.05 | 1.113 \* |
| LSD value | 3.591 \* | 2.596 NS | 0.214 NS | --- |
| \* (P<0.05). |

Eosinophil and Basophil evaluation shows no significant difference neither between age groups nor between treatment groups. As shown in table 3 and 4.

**Table 3. Effect of Treatment and age groups in Basophile**

|  |  |  |
| --- | --- | --- |
| Age groups (year) | Mean ± SE of Basophile % | ANOVA value |
| Pre-Treatment  | Post-Treatment | Control |
|  1-15 | 0.597 ± 0.51 | 0.473 ± 0.27 | 0.042 ± 0.01  | 0.967 NS |
| 16-40 | 0.272 ± 0.10 | 0.200 ± 0.07 | 0.064 ± 0.01 | 0.211 NS |
| 41-65 | 1.717 ± 0.30 | 0.151 ± 0.07 | 0.084 ± 0.01 | 0.736 NS |
| 66 and above | 0.159 ± 0.08 | 0.158 ± 0.05 | 0.081 ± 0.01 | 0.162 NS |
| LSD value | 0.978 NS | 0.431 NS | 0.040 \* | --- |
| \* (P<0.05). |

**Table 4. Effect of Treatment and age groups in Eosinophil**

|  |  |  |
| --- | --- | --- |
| Age groups (year) | Mean ± SE of Eosinophil % | ANOVA value |
| Pre-Treatment  | Post-Treatment | Control |
|  1-15 | 0.178 ± 0.03 | 0.152 ± 0.03 | 0.167 ± 0.03 | 0.082 NS |
| 16-40 | 0.158 ± 0.02 | 0.140 ± 0.03 | 0.201 ± 0.01 | 0.068 NS |
| 41-65 | 0.142 ± 0.03 | 0.124 ± 0.02 | 0.176 ± 0.04 | 0.103 NS |
| 66 and above | 0.116 ± 0.02 | 0.154 ± 0.02 | 0.183 ± 0.02 | 0.061 \* |
| LSD value | 0.076 NS | 0.075 NS | 0.087 NS | --- |
| \* (P<0.05). |

A heightened percentage of monocytes in the blood caused by:

* chronic inflammatory disease, such as inflammatory bowel disease
* a parasitic or viral infection
* a bacterial infection
* a collagen vascular disease, such as lupus, vasculitis, or rheumatoid arthritis
* Certain types of leukemia12.

At (2017) it`s observed that monocyte‑depleted peripheral blood lymphocytes from healthy donors could be used to generate large numbers of CD3+CD8+ CTLs through immune stimulation. These CD3+CD8+ CTLs could effectively recognize and induce the apoptosis of human Kasumi‑3 AML cells. Which agrees with our results that show regression in monocyte cout post treatment. In addition, cytarabine‑induced AML cell apoptosis was enhanced by CTL treatment. Western blotting revealed that Bcl‑2 expression was downregulated in AML cells following cytarabine and CTL treatment, indicating that the synergistic effect of this treatment on AML cell apoptosis is due to the downregulation of Bcl‑2 13.

 One of the main symptoms for AML patients is the bleeding tendency according to14 that agree with our observations a case of severe central nervous system bleeding in a patient with acute monocytic leukemia. The patient was admitted to their emergency department because of massive back pain and positive meningeal signs. MR imaging yielded a spontaneous epidural hematoma of the thoracic vertebral column. Coagulation studies revealed fibrinogen levels below the linear measuring range and blood smears showed myeloid blast cells in the peripheral blood. The diagnosis of acute monocytic leukemia was confirmed by flow cytometric analysis. Despite of substitution with more than 12 g fibrinogen per day over 3 days plasma fibrinogen levels couldn’t be stabilized. After starting the induction chemotherapy with cytarabine, laboratory coagulation test results were improved. Despite all intensive medical efforts, the patient died due to cerebral epidural hematoma.

One such cytogenetic abnormality is the pericentric inversion (inv) of chromosome 16 which is typically seen in AML M4 with eosinophilia and is associated with a favorable prognosis. They report the inv (16) in a young woman with AML M5 and abnormal eosinophils. This is a rare entity with only about 20 cases reported until date15. Which differs from this study outcome in eosinophil aspect.

Another evaluation of peripheral blood and bone marrow for an indication of persistent eosinophilia can be a challenging task because there are many causes of eosinophilia and the morphologic differences between reactive and neoplastic causes are often subtle or lack specificity. The purpose of this review is to provide an overview of the differential diagnosis for eosinophilia, to recommend specific steps for the pathologist evaluating blood and bone marrow, and to summarize two important causes of eosinophilia that require specific ancillary tests for diagnosis: myeloproliferative neoplasm with PDGFRA rearrangement and lymphocytevariant hypereosinophilic syndrome16.

The ranges of blood cell count below are for adults. They may be a little different from lab to lab and for children and teens. Differential (also called diff) (Shows the part of the blood made up of different types of white cells (The types of white cells counted are neutrophils, lymphocytes, monocytes, eosinophils and basophils. (Adults usually have about 60% neutrophils, 30% lymphocytes, 5% monocytes, 4% eosinophils and less than 1% basophils in the blood17 and that may explain our results that show no significant difference in monocyte, eosinophil and basophil count.

Acute basophilic leukemia with U2AF1 mutation reported by18.

Flowcytometry could identify these markers with their distinct appearance in Basophils gate (i.e. Moderate CD45 which was dimmer than Lymphocytes and brighter than myeloblast gate) and positivity of the following markers CD34, CD117, CD13, CD33, CD22, and CD9 &CD25 on this population denoting Bsophilic differentiation. Upon reviewing the literature only few rare cases describing such abnormal combination is found. The second challenge arose when the FISH result showed positive Philadelphia chromosome, the question was whether it is Blast crisis of CML or De-novo AML with positive Ph. Chromosome19. Which agree with our results that found patients CD34+ with normal Basophil count.

Myelodysplastic syndrome (MDS) terminally transforms to acute myeloid leukemia (AML) or bone marrow failure syndrome, but acute myeloid leukemia with basophilic differentiation has been rarely reported. An 81-year-old man was referred for further examination of intermittent fever and normocytic anemia during immunosuppressive treatment. Chromosomal analysis showed additional abnormalities involving chromosome 7. He was diagnosed as having MDS. At the time of diagnosis, basophils had not proliferated in the bone marrow. However, his anemia and thrombocytopenia rapidly worsened with the appearance of peripheral basophilia three months later. He was diagnosed as having AML with basophilic differentiation transformed from MDS. At that time, monosomy 7 was detected by chromosomal analysis. Basophils can be confirmed on the basis of the positivity for CD203c and CD294 by flow cytometric analysis. By cytogenetic analysis they find that that basophils were derived from myoblasts20.

Another rare case reported of acute basophilic leukemia with t(16;21)(p11;q22) generating the FUS-ERG fusion gene. The basophilic nature of leukemia blasts were demonstrated by cytomorphology, toluidine blue metachromasia, mature basophil-associated antigen expression, and characteristic granules under electron microscopy. The molecular link between t(16;21)/FUS-ERG and basophilic differentiation remains unclear21.

Acute basophilic leukemia with add (3)(q12) accompanied by histamine excess symptoms22.

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