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RESEARCH ARTICLE

PANCYTOPENIA AS INITIAL PRESENTATION OF ACUTE LYMPHOBLASTIC LEUKEMIA AND ITS ASSOCIATIONWITH BONE MARROWRESPONSE

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Abstract

Objective: The objective of this study is to determine the frequency of pancytopenia and bone marrow response to treatment of acute lymphoblastic leukemia.

Materials And Methods: This is a cross sectional study carried out at Medical Oncology Department, Hayatabad Medical Complex, Peshawar. A total of 120 patients were included in the study. Venous blood sample was obtained from patients and sent to the laboratory of the hospital for assessment of red blood cells, white blood cells, and platelets. Reports were assessed and levels were noted. If levels were lower than normal, then patients were labeled as having pancytopenia was labeled.Patients were advised treatment i.e drug regimen including weekly intravenous vincristine, daunorubicin, weekly intrathecal methotrexate and daily dexamethosone for 4 weeks). After 4 weeks they underwent bone marrow aspiration. All samples were sent to the laboratory of the hospital for assessment of bone marrow response i.e M1 (less than 5% lymphoblasts), M2 (5% to 25% Lymphoblasts)& M3 (more than 25% Lymphoblasts).

Results: Pancytopenia was recorded in 35 (29.16%) patients presenting with acute lymphoblastic leukemia. Out of these thirty-five patients, 21 (60%) were male and 14(40%) were female. Out the 21 males, 20 (95.24%)hadM1 responsewhile0 1(4.76%)patienthadM2response. Out of the14female patients,12(85.71 %)hadM1 response, 1(7.14 %) had M2 and 1(7.14%) had M3 response. Out of the 85 patients who did not have pancytopenia, 50 (58.8%) were male and 35 (41.2%) were female. Out of the 50 males withoutpancytopenia,36(72%) hadM1,10(20%)hadM2and4(8%) hadM3response.Among the 35 female patients, 31(88.57%) had M1, 2(5.71%) had M2 and 2(5.71%) had M3 response.

Conclusion: The study concluded that although pancytopenia is a fairly common presentation of acute lymphoblastic leukemia but there is no significant difference in the outcome of patients receiving treatment for acute lymphoblastic leukemia in association with presence or absence of pancytopenia as initial presentation or with respect to duration of the disease.

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Introduction:-

Acute lymphoblastic leukemia is a malignant disorder of lymphoid progenitor cells, resulting from neoplastic transformation of lymphoid stem cells due to altered genome of the stem cells [1]. There is lack of differentiation beyond blast stage and progressive accumulation of leukemic blasts in the bone marrow with resultant suppression of normal hematopoiesis leading to anemia, thrombocytopenia and neutropenia [2].

Diagnosis of cytopenias can be challenging as it is difficult to distinguish between bone marrowfailure due to disease progression and autoimmunity [3].A preleukaemic phase, typified by transient pancytopenia, is a rare occurrence that usually affects children and adolescents developing Acute Leukemia [4].

Pancytopenia is a condition where there is a decrease in all the three formed elements of the blood: red blood cells, white blood cells, and platelets [5]. Criteria for diagnosis of pancytopenia being hemoglobin <10 g/dL, total leukocyte count <3,500/µL and platelet count < 100,000/µL. Pancytopenia can be caused in a number of conditions leading to diagnostic dilemma [5].

Kulkarni Kp reported in a study that pancytopenia is an independent predictor of improved survival in patients with Acute Lymphoblastic Leukemia [6].Raja S et al has reported that the frequency of pancytopenia was 12.4% in patients with Acute Lymphoblastic Leukemia [7].Among patients with Acute Lymphoblastic Leukemia,bone marrow responseto treatment is reported as M1 (<5% lymphoblasts) in 61.5%, M2 (5-25% lymphoblasts) in 25.5% and M3 (>25% lymphoblasts) in 13% patients [8].

Literature showed limited data regarding occurrence of pancytopenia and bone marrow response to treatment in patients with Acute LlymphoblasticLeukemia. This study was conducted to determine the frequency of pancytopenia in newly diagnosed Acute Lymphoblastic Leukemiapatients and bone marrow response to treatment forin local population. It can help to identify and rectify the problems in time in order to prevent complications and further deterioration of clinical condition of patients.

Objective:-

The rationale of this study is to determine the frequency of pancytopenia and bone marrow response to treatment of acute lymphoblastic leukemia.

Materials And Methods:-

Study design:
Cross sectional study.

Setting:
Department of Medical Oncology, Hayatabad Medical Complex, Peshawar, Pakistan.

Study duration:
01-08-2021 to 31-1-2022

Sample size:
120 patients

Sampling technique:
Non-probability, consecutive sampling.

Inclusioncriteria:
Patients of age 05-50 years of either gender presenting with newly diagnosed Acute Lymphoblastic Leukemia.

Written informed consent taken from patients above 18 years ofage.

In case of minors, consent shall be taken from parents or guardian.

Exclusion criteria:
Other concomitant malignancy (on medicalrecord).
Patients takingradiotherapy.
Patients already taken treatment for leukemia (medicalrecord).

Data Analysis:
Data was analyzed by SPSS version 27.0. Quantitative variables like age and duration of Acute Lymphoblastic Leukemia were calculated as mean and standard deviation. Qualitative variables like gender, pancytopenia and bone marrow response to Acute Lymphoblastic Leukemia treatment were presented as frequency and percentage. Data was stratified for age, gender, duration of Acute Lymphoblastic Leukemia. Post-stratification, chi- square was applied to compare pancytopenia and bone marrow response in stratified groups by using chi-square test for each stratum. P-value≤0.05 was considered assignificant.

Results:-

Total of 120 patients were included in the study. Age ranged between5-50 years with mean and SDs 13+10.12. Mean and SDs for duration of disease was 5+1.23 weeks. Out the total patients, 104 (86.66%) patients were in 5-25 years whereas 16 (13.34%) patients were in 26-50 years age group. Number of male patients were 71 (59.16%) and female were 49 (40.84%). Pancytpenia was recorded in 35 (29.16%) patients presenting with Acute Lymphoblastic Leukemia.As per bone marrow response to treatment, 99 (82.5%) were in M1 category, 14 (11.66%) patients were in M2 category while 07 (5.83%) patients were in M3 category.

Pancytopenia was stratified with age, gender, duration of disease and bone marrow response to treatment in (Tables No. 1,2&3 respectively).

Table1:- Stratification of Pancytopenia with respect to Age & Gender (n=120).

Age Group				
Age	**Pancytopenia**	**Frequency**	**%age**	**P-value**
05-25 Years	Yes	32	26.66%	0.324
	No	72	60%	
26-50 Years	Yes	03	02.5%	
	No	13	10.83%	
Gender ↓ Gender Groups				
Male	Yes	21	17.5%	0.905
	No	50	41.66%	
Female	Yes	14	11.66%	
	No	35	29.16%	

Table 2:- Stratification of Pancytopenia with respect to duration of disease (n=120).

Duration	**Pancytopenia**	**Frequencies**	**Percentages**	**P Value**
< 6 weeks	Yes	30	25%	0.070
	No	81	67.5%	
> 6 weeks	Yes	05	4.16%	
	No	04	3.33%	

Table 3:- Stratification of pancytopenia with respect to Bone Marrow Response (n=120).

Response	**Pancytopenia**	**Frequencies**	**Percentages**	**P-value**
M 1	Yes	32	26.66%	0.255
	No	67	55.83%	
M 2	Yes	02	1.66%	
	No	12	10%	
M 3	Yes	01	0.83%	
	No	06	5%	

Discussion:-

Acute lymphoblastic leukemia (ALL) is a malignant (clonal) disease of the bone marrow inwhich early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow. ALL is the most common type of cancer and leukemia in children in the United States. The malignant cells of acute lymphoblastic leukemia (ALL) are lymphoid precursor cells (i.e., lymphoblasts) that are arrested in an early stage of development. This arrest is caused by an abnormal expression of genes, often as a result of chromosomal translocations or abnormalitiesof chromosome number.

These aberrant lymphoblasts proliferate, reducing the number of the normal marrow elements that produce other blood cell lines (red blood cells, platelets, and neutrophils). Consequently, anemia, thrombocytopenia, and neutropenia occur, although typically to a lesserdegree than is seen in Acute Myeloid Leukemia. Lymphoblasts can also infiltrate organs other than the bone marrow, particularly the liver, spleen, and lymph nodes, resulting in enlargement of these organs. A review of the genetics, cell biology, immunology, and epidemiology of childhood leukemia byGreaves concluded that B-cell precursor acute lymphoblastic leukemia (ALL) has a multifactorial etiology, with a two-step process of genetic mutation and exposure to infection playing a prominent role. The first step occurs in utero, when fusion gene formation or hyperdiploidy generates a covert, pre-leukemic clone. The second step is the postnatalacquisition of secondary genetic changes that drive conversion to overt leukemia. Only 1% ofchildren born with a pre-leukemic clone progress to leukemia [9].The second step is triggered by infection. Triggering is more likely to occur in children whoseimmune response is abnormally regulated because they were not exposed to infections in the firstfew weeks and months of life. Lack of exposure to these early infections, which primes theimmune system, is more likely to occur in societies that are zealous about hygiene; this wouldhelp explain why at present, pediatric ALL is seen primarily in industrialized societies.Less is known about the etiology of ALL in adults, compared with acute myeloid leukemia(AML). Most adults with ALL have no identifiable risk factors.Although, most leukemias occurring after exposure to radiation are AML rather than ALL, anincreased prevalence of ALL was noted in survivors of the Hiroshima atomic bomb but not inthose who survived the Nagasaki atomic bomb. Acute lymphoblastic leukemia (ALL) is the most common type of cancer and leukemia inchildren in the United States. Median age at diagnosis is 16 years. ALL accounts for 74% ofpediatric leukemia cases [10].

In adults, ALL is less common than acute myeloid leukemia (AML). The American CancerSociety estimates that 6150 cases of ALL (adult and pediatric) will occur in the United States in2020, resulting in 1520 deaths. The estimated 5-year survival is 68.6%. The favorable survival rate is due to the high cure rate of ALL in children. Prognosis declines with increasing age, andthe median age at death is 56 years [11].

Only 20-40% of adults with acute lymphoblastic leukemia (ALL) are cured with currenttreatment regimens.Historically patients with ALL were divided into three prognostic groups: good risk,intermediate riskand poor risk. The addition of tyrosine kinase inhibitors to chemotherapy has resulted in improved prognosis of patients with Philadelphia chromosome–positive ALL such that many experts no longer considerthese patients as having poor risk.Casespecific molecular probes or multiparametric flow cytometry can be used to detect one leukemic cell in 10,000 mononuclear cells (ie, sensitivity of $>10^4$) [12]. The presence of such minimalresidual disease (MRD) after treatment is a strong predictor for relapse.Meta-analysisof 39 trials of ALL treatment of children and adults demonstrated that the eventfreesurvival (EFS) hazard ratio for achieving MRD negative status after therapy was 0.23 forpediatric patients and 0.28 for adults. The hazard ratio for overall survival was 0.28 for bothpatient populations. The effect was seen across therapies, disease subtypes and methods ofdetection. Cause of cytopenias can be difficult to diagnose since it is difficult to distinguish between bone marrow loss caused by disease progression and autoimmunity. A preleukaemic phase, characterised by temporary pancytopenia, is an uncommon condition that often affects children and teenagers.The major risk factors are the genetic abnormalities and treatment responses.

In line with the current study, Czuczman MS et al reported that neoplasia had the highest rate of new onset pancytopenia in adults with 65% of the related cases [13]. Similar to the previous study, Pei JS et al also revealed that megaloblastic anemia was the most common cause of pancytopenia followed by malaria in 19% with pancytopenia[14].

The current study finding was consistent with those of the previous study by Rosenberg AS et al in Iranian population [15]. The low frequency of latter causes indicates that there might be different etiological patterns based on geographical population. In contrast to the current study, Berry DA et alreported the frequency of 19% for

malaria (2nd most common cause) in Indian population, which seems to be endemic in subcontinent countries[16].Similar findings in the study by Harrison CJ et al., on 100 patients with pancytopenia showed infections (20%) and hypersplenism (15%) were the 2nd and 3rd most common causes of pancytopenia[17]. The majority of patients in the study were above 40 years old, 421(63.3%) cases. However, the study by Arber DA et al revealed that most of the patients were in age group of 11-30 years[18]. It was observed that 97 (14.6%) cases with pancytopenia were below 20 years old and the most common causes of pancytopenia in this age group was acute leukemia detected in 56 (23.8%) casesfollowed by aplastic anemia in 18(29.5%) [19].

The current study findings were consistent with those of Zhang J et al on 279 pancytopenic 5 -25 years old that revealed acute leukemia was the commonest cause of pancytopenia identified in 32.2% of the cases, followed by aplastic anemia 30.8%[20]. However, Srivastava S et al demonstrated that among young patients under 18 years old, aplastic anemia was the most prevalent cause of pancytopenia (43%), and the 2nd most common cause was acute leukemia identified in 25% of the cases[21].

Conclusion:-

Although pancytopenia is a fairly common presentation of acute lymphoblastic leukemia but there is no significant difference in the outcome of patients receiving treatment for acute lymphoblastic leukemia in association with presence or absence of pancytopenia as initial presentation or with respect to duration of the disease.

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