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EVALUATION OF THERAPEUTIC STRATEGIES AND OUTCOMES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AT HAYATABAD MEDICAL COMPLEX, PESHAWAR

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Abstract

Background: Chronic Lymphocytic Leukemia (CLL) is characterized by the clonal proliferation of mature, dysfunctional B-lymphocytes, leading to peripheral leukocytosis, bone marrow failure, and complications such as anemia, recurrent infections, and organomegaly. Evaluating treatment efficacy in local settings is crucial for optimizing patient management. Therefore, the purpose of this study was to assess the impact of standard therapeutic regimens on hematological and biochemical parameters in CLL patients at a tertiary care hospital in Peshawar.

Methods: A comparative cross-sectional study was conducted at Hayatabad Medical Complex (HMC). Seventy-three (n=73) adult patients (≥40 years) with diagnosed CLL were enrolled via consecutive sampling. Data on demographics, treatment regimens, and pre- and post-treatment laboratory parameters were collected. Venous blood samples were analyzed for complete blood counts and biochemical profiles using

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standardized automated analyzers. Statistical analysis was performed using SPSS version 26.; paired sample t-tests were used to compare pre- and post-treatment means.
Results: The cohort comprised 74% males and 26% females. Dexamethasone (86.3%) and Bendamustine (61.6%) were the most frequently administered agents. Post-treatment analysis revealed significant improvements: a substantial reduction in total white blood cell count (mean: 358.63 to 193.13 x10^3/µL, p=0.001) and absolute lymphocyte count (mean: 53.30% to 38.24%, p<0.001). Bone marrow blast percentage decreased significantly (0.21% to 0.01%, p=0.001). Serum Lactate Dehydrogenase (LDH) levels also decreased significantly (217.44 to 189.53 U/L, p=0.007).
Conclusion: The therapeutic strategies, predominantly based on Bendamustine and Dexamethasone, were effective in achieving significant cytoreduction and improving key disease markers in CLL patients. The findings align with regional treatment patterns and demonstrate the efficacy of these protocols in a real-world setting.

INTRODUCTION

Leukemia represents a heterogeneous group of hematologic malignancies originating from the malignant transformation of hematopoietic stem cells within the bone marrow, characterized by the unregulated proliferation and accumulation of immature or abnormal leukocytes [1]. These disorders disrupt normal hematopoiesis, leading to bone marrow failure and the infiltration of extramedullary sites. Among the leukemias, Chronic Lymphocytic Leukemia (CLL) stands as the most prevalent adult leukemia in Western populations, accounting for approximately 25-35% of all leukemia cases in regions like North America and Europe [2, 3]. CLL is a clinically heterogeneous B-cell lymphoproliferative disorder defined by the progressive accumulation of monoclonal, immunologically dysfunctional but morphologically mature CD5+ B-lymphocytes in the peripheral blood, bone marrow, lymph nodes, and spleen [4].
The clinical trajectory of CLL is remarkably variable. A significant proportion of patients are asymptomatic at diagnosis, with the condition discovered incidentally during routine blood tests that reveal absolute lymphocytosis [5]. For others, the disease presents with symptoms related to bone marrow infiltration (such as anemia, thrombocytopenia, and neutropenia), constitutional B-symptoms (fever, night sweats, unintended weight loss), or lymphoproliferative manifestations including lymphadenopathy and hepatosplenomegaly [6]. The diagnosis is firmly established through a combination of persistent peripheral blood B-cell lymphocytosis (≥5 x 10^9/L) and a characteristic immunophenotypic profile typically CD5+, CD19+, CD20(dim), CD23+, with weak surface immunoglobulin expression confirmed by multiparameter flow cytometry, as per the International Workshop on CLL (IWCLL) criteria [7].
Management strategies for CLL are not initiated universally at diagnosis but are guided by the presence of active or symptomatic disease, alongside comprehensive risk stratification incorporating clinical staging (Rai or Binet systems) and molecular prognostic markers such as IGHV mutation status, cytogenetic abnormalities (e.g., del(17p), del(11q)), and TP53 mutation status [8]. The treatment landscape has undergone a revolutionary transformation over the past two decades.

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Historically, therapy was limited to alkylating agents like chlorambucil. This evolved to include purine analog-based chemoimmunotherapy regimens, such as Fludarabine, Cyclophosphamide, and Rituximab (FCR), which became the gold standard for fit, younger patients [9]. More recently, a paradigm shift has occurred with the introduction of novel targeted agents that inhibit key survival pathways in CLL cells. These include Bruton's tyrosine kinase (BTK) inhibitors (e.g., Ibrutinib, Acalabrutinib), which disrupt B-cell receptor signaling, and the BCL-2 inhibitor Venetoclax, which promotes apoptosis [10]. These agents have demonstrated superior efficacy and more favorable toxicity profiles compared to traditional chemotherapy, particularly in high-risk genetic subgroups.

In Pakistan, like many other low- and middle-income countries, the management of CLL faces unique challenges. While epidemiological data suggest a lower incidence compared to Western nations, CLL remains a significant clinical entity in hematology-oncology practice [11]. However, data on real-world treatment patterns, accessibility to modern therapeutics, and clinical outcomes are scarce and fragmented. Previous studies from Pakistan have primarily focused on describing the clinico-hematological profile at diagnosis [12, 13]. There is a paucity of published literature systematically evaluating the therapeutic outcomes of CLL patients following intervention in the local context. This gap in knowledge impedes the development of context-specific treatment guidelines and resource allocation strategies. Therefore, this study aimed to evaluate the therapeutic strategies employed and their hematological and biochemical impact on CLL patients managed at Hayatabad Medical Complex, Peshawar, a major tertiary care referral center. By analyzing pre- and post-treatment parameters, this research seeks to contribute valuable real-world evidence on the effectiveness of prevailing treatment protocols and highlight areas for improvement in the management of CLL in Pakistan.

Materials and Methods

A comparative cross-sectional study was conducted at the Hayatabad Medical Complex (HMC) in Peshawar from July to December 2024. Seventy-three patients diagnosed with CLL were enrolled via consecutive sampling. Inclusion criteria required patients to be ≥40 years with a confirmed CLL diagnosis per IWCLL criteria [7]. Ethical approval was obtained from the relevant Institutional Review Boards, and written informed consent was secured.

Data on demographics, treatment details, and laboratory parameters were collected. Pre-treatment and post-treatment venous blood samples were analyzed. Complete blood counts were performed on EDTA samples using an automated hematology analyzer. Biochemical parameters (urea, creatinine, LDH, SGPT, etc.) were analyzed from serum using a Cobas c6000 chemistry analyzer (Roche Diagnostics).

Statistical analysis was performed using SPSS version 26.0. Descriptive statistics were computed. A paired-sample t-test was used to compare pre- and post-treatment laboratory parameters, with $p<0.05$ considered significant.

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Results

Demographic and clinical characteristics

The study included 73 CLL patients. The cohort was predominantly male (74%). The age distribution was nearly equal between patients aged 40-60 years (49.3%) and those above 60 years (50.7%). More than half of the patients (58.9%) required packed red blood cell transfusion during their management course (Table 1).

Table 1: Demographic and Clinical Characteristics of CLL Patients (n=73)

Characteristic	Category	Frequency (n)	Percentage (%)
Gender	Male	54	74.0
	Female	19	26.0
Age Group	40-60 years	36	49.3
	>60 years	37	50.7
Transfusion Requirement	Yes	43	58.9
	No	30	41.1

Therapeutic Regimens Administered

Dexamethasone was the most administered agent (86.3%), followed by Bendamustine (61.6%). Other chemotherapeutic agents like Cyclophosphamide and Fludarabine were used less frequently. The use of novel targeted therapy (Ibrutinib) was minimal (1.4%). Rituximab and Chlorambucil were not used in this cohort (Table 2).

Table 2: Frequency of Therapeutic Agents Administered to CLL Patients (n=73)

Therapeutic Agent	Frequency (n)	Percentage (%)
Dexamethasone	63	86.3
Bendamustine	45	61.6
Cyclophosphamide	16	21.9

Therapeutic Agent	Frequency (n)	Percentage (%)
Fludarabine	13	17.8
Methylprednisolone	12	16.4
Ibrutinib	1	1.4

Impact of Treatment on Hematological Parameters

Post-treatment analysis showed significant improvements in key hematological indices (Table 3). There was a marked and statistically significant reduction in the total White Blood Cell (WBC) count ($p=0.001$) and the absolute lymphocyte percentage ($p<0.001$). The bone marrow blast percentage also decreased significantly ($p=0.001$). Although not statistically significant, improving trends were observed for hemoglobin levels and platelet counts. The neutrophil percentage increased significantly post-treatment ($p<0.001$).

Table 3: Comparison of Hematological Parameters Pre- and Post-Treatment (n=73)

Parameter	Pre-Treatment Mean (SD)	Post-Treatment Mean (SD)	p-value
Hemoglobin (g/dL)	11.02 (2.66)	11.25 (2.94)	0.244
WBC Count ($x10^3/\mu L$)	358.63 (70.71)	193.13 (43.00)	**0.001**
Neutrophils (%)	36.21 (25.18)	48.60 (25.46)	**<0.001**
Lymphocytes (%)	53.30 (27.98)	38.24 (27.24)	**<0.001**
Platelets ($x10^3/\mu L$)	170.25 (89.34)	176.21 (95.28)	0.497
Bone Marrow Blast (%)	0.2055 (0.526)	0.0137 (0.117)	**0.001**

Impact of Treatment on Biochemical Parameters

Among the biochemical markers, a significant decrease was observed in serum Lactate Dehydrogenase (LDH) levels post-treatment ($p=0.007$). Other parameters, including renal function

tests (urea, creatinine), liver enzymes (SGPT, ALP), and electrolytes, did not show statistically significant changes (Table 4).

Table 4: Comparison of Biochemical Parameters Pre- and Post-Treatment (n=73)

Parameter	Pretreatment Mean (SD)	Posttreatment Mean (SD)	p-value
Urea (mg/dL)	27.76 (14.28)	28.01 (17.43)	0.904
Creatinine(mg/dL)	2.067 (10.085)	1.974 (9.386)	0.304
SGPT/ALT (U/L)	26.76 (18.32)	27.10 (17.00)	0.849
ALP (U/L)	126.97 (135.71)	120.86 (96.59)	0.343
LDH (U/L)	217.44(125.27)	189.53 (88.42)	**0.007**
Uric Acid (mg/dL)	4.155 (2.878)	4.129 (2.734)	0.876
Calcium (mg/dL)	7.349 (3.479)	7.238 (3.446)	0.057
Sodium (mmol/L)	122.43 (43.47)	122.41 (43.44)	0.972
Potassium (mmol/L)	3.913 (1.541)	3.778 (1.519)	0.177
Chloride (mmol/L)	92.41 (32.91)	93.19 (33.51)	0.348

Discussion

This study provides a comprehensive evaluation of the therapeutic strategies and their associated hematological and biochemical outcomes in CLL patients managed at a major tertiary care center in Peshawar, Pakistan. Our findings offer crucial insights into the real-world management of CLL within the constraints of a resource-limited healthcare setting.

The demographic profile observed in our cohort a pronounced male predominance (74%) with a nearly equal distribution between patients aged 40-60 and those above 60 years, is consistent with the established epidemiology of CLL both globally and within the South Asian region. A systematic review of CLL in Pakistan by Ammad Ud Din et al. (2023) reported a mean age of 59 years across studies and a consistent male preponderance, aligning closely with our findings [11]. Similarly, a large prospective study from India by Tejaswi et al. (2020) reported a median age of 61 years and a male-to-female ratio of 2.4:1, further corroborating the demographic trends seen in our population

[14]. The high proportion of patients (58.9%) requiring red cell transfusion underscores the significant burden of disease-related anemia at presentation or during treatment, a common complication due to bone marrow infiltration and, at times, autoimmune hemolytic anemia [15].

The analysis of treatment patterns reveals a clear reliance on chemotherapeutic and corticosteroid-based regimens. Dexamethasone, utilized in 86.3% of patients, and Bendamustine, in 61.6%, were the cornerstones of therapy. This pattern aligns with practices reported from other major cancer centers in Pakistan. For instance, a study from Shaukat Khanum Memorial Cancer Hospital by Nazir et al. (2016) reported that the Fludarabine and Cyclophosphamide (FC) combination was the most common first-line regimen (83%), with a smaller proportion receiving FCR (11%) [16]. The high usage of corticosteroids like dexamethasone, while effective for symptom control and as part of anti-neoplastic combinations, warrants attention due to potential long-term side effects including immunosuppression, hyperglycemia, and osteoporosis [17].

The most striking finding, however, is the near absence of novel targeted therapies and monoclonal antibodies. Ibrutinib was administered to only one patient (1.4%), and Rituximab was not used at all during the study period. This stands in stark contrast to contemporary international guidelines, which position BTK inhibitors (e.g., Ibrutinib) and BCL-2 inhibitors (e.g., Venetoclax), often with or without CD20 antibodies, as preferred first-line and relapse therapies for most patient groups due to superior progression-free survival and a more favorable toxicity compared to chemoimmunotherapy [10,18]. This disparity highlights a critical "therapeutic gap" and underscores the profound challenges related to drug cost, availability, and insurance reimbursement in low- and middle-income countries (LMICs) like Pakistan. Giri et al. (2021) have extensively documented these access barriers to novel drugs for CLL in LMICs, which significantly impact treatment outcomes and survival [19].

The efficacy analysis demonstrated that the employed regimens were successful in achieving significant cytoreduction. The dramatic reduction in total WBC count (mean decrease of 165.5 $x10^3/\mu L$, $p=0.001$) and absolute lymphocyte percentage (mean decrease of 15.06%, $p<0.001$) indicates a robust treatment response. These results are comparable to outcomes reported with traditional chemotherapy in other local studies. For example, Zeeshan et al. (2015) reported a mean WBC count of 82.9 $x10^3/\mu L$ in their CLL cohort at presentation, and treatment would be expected to reduce this significantly [13]. Similarly, the significant decrease in bone marrow blast percentage post-treatment is a key indicator of morphological remission [7].

The significant reduction in serum LDH levels ($p=0.007$) is another important finding. LDH is a recognized biomarker of high tumor burden and cellular turnover in lymphoproliferative disorders [20]. Its decrease correlates with effective disease control. While our study did not find significant changes in other biochemical parameters like creatinine or SGPT, this is not unexpected as these are not direct markers of CLL disease activity but can be affected by treatment toxicity or comorbidities. The improving, though non-significant, trends in hemoglobin and platelet counts suggest a recovery of bone marrow function, which often lags the reduction in lymphocyte count.

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Limitations and Future Directions

This study has several limitations. Its cross-sectional design precludes the assessment of long-term outcomes such as overall survival, progression-free survival, duration of response, and treatment-related toxicity profiles, which are critical for a complete evaluation of any therapeutic strategy. The single-center nature may limit the generalizability of the findings to other regions of Pakistan with different resource availabilities. A major limitation is the lack of data on cytogenetic and molecular risk stratification (e.g., IGHV status, del(17p), TP53 mutations), which are pivotal in predicting treatment response and guiding therapy selection in the modern era.

Future research should focus on multicenter, prospective longitudinal studies that incorporate comprehensive prognostic testing. There is an urgent need for health economic studies and policy advocacy to improve access to targeted therapies in Pakistan. Investigating the feasibility and outcomes of alternative dosing or access programs for expensive novel agents could be a valuable area of exploration.

Conclusion

The therapeutic strategies were effective in achieving significant cytoreduction and improving key hematological and biochemical disease markers in CLL patients. The findings validate the continued efficacy of these conventional chemotherapeutic protocols within the local context and align with historical regional practices. However, the study starkly highlights a substantial and concerning gap in access to contemporary targeted therapies that define modern, precision-based CLL management globally. Bridging this "therapeutic gap" is imperative to align patient care in Pakistan with international standards.

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