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Original Article

INVESTIGATION OF STRESS AND INFLAMMATORY MARKERS IN ACUTE LEUKEMIA BEFORE AND AFTER CHEMOTHERAPY

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ABSTRACT

Chemotherapy affects biomarkers linked to inflammation and stress and is essential in the treatment of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). This study compared the levels of cortisol, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) in patients with AML and ALL before and after chemotherapy. This study includes 20 AML patients and 14 ALL individuals. To evaluate the levels of TNF-α, IL-6, cortisol, and CRP, blood samples were taken both before and after chemotherapy. Standard error of the mean (SEM) and paired t-test were used to statistically assess the data. A significance level of $P < 0.05$ was established. The findings showed that CRP levels significantly decreased in both AML ($P = 0.010$) and ALL ($P = 0.004$), suggesting a reduction in systemic inflammation. In ALL ($P = 0.008$) and AML ($P < 0.001$), cortisol levels also considerably decreased, indicating a decrease in physiological stress. Both leukemia types exhibited significant reductions in pro-inflammatory cytokines TNF-α and IL-6 ($P < 0.05$), indicating the importance of treatment in reducing inflammatory responses. These results demonstrate how well chemotherapy effectively reduces inflammatory and stress biomarkers in acute leukemia patients, demonstrating its anti-inflammatory and stress-reducing benefits.

Keywords: Inflammation, Stress, Chemotherapy, Acute lymphoblastic leukemia, Acute myeloid leukemia

1. INTRODUCTION

Malignant clonal disorders of the blood-forming organs, acute leukemias are defined by the replacement of bone marrow by aberrant immature cells, which results in a decrease in platelets and erythrocytes. Recent revisions have integrated cytogenetic and molecular anomalies, and they are categorized according to the origin of aberrant hematopoietic cells, such as lymphoid (ALL) or myeloid (AML) (Park, 2024). There are difficulties in diagnosing and treating mixed-phenotype acute leukemia (MPAL), an uncommon type that has both myeloid and lymphoid characteristics (Khan et al., 2018). Chromosome translocations cause ALL, the most prevalent pediatric cancer (Mrózek et al., 2004), whereas the buildup of aberrant immature cells causes AML, which frequently leads in bone marrow failure (Shimony et al., 2023). Proinflammatory cytokines such as TNF-α and IL-6 are higher in leukemic patients, suggesting an inflammatory state associated with carcinogenesis (Giordano et al., 2010). Chronic inflammation contributes to the development of cancer, and neutrophils help tumors grow by secreting growth factors and cytokines (Templeton et al., 2014). An inflammatory marker called CRP is linked to the development and risk of cancer (Iivanainen et al., 2019). According to (Ke et al., 2020), IL-6, which raises CRP levels, is similarly connected to unfavorable results with cancer immunotherapy. Stress hormone cortisol affects cancer outcomes and immunological function (Cash et al., 2024). Remission-induction, consolidation, and maintenance therapy are all part of the treatment for ALL, and they frequently have negative side effects include hepatotoxicity and myelosuppression (Jayachandran et al., 2014). Daunorubicin and cytarabine are frequently administered during the treatment of AML, with total remission being achieved by 70%-75% of patients (Burnett et al., 2011). Improvements in flow cytometry have contributed to better diagnosis of AML, which has prognostic and classification implications (Lucas & Hergott, 2023). To analyze the role of stress (cortisol) and inflammation (CRP, IL-6, and TNF-α) in the prognosis, resistance, and chemotherapy-induced toxicity, this research evaluates the changes in amount of these markers in acute leukemia patients compared to a healthy matched sample before and after chemotherapy (Shimony et al., 2023).

2. PATIENTS AND METHODS

Study Population

The study was observational, comparative analysis designed to investigate the levels of stress-related (cortisol) and inflammatory markers (CRP, IL-6, and TNF-α) in patients newly diagnosed with acute leukemia both before and after chemotherapy. Patients who had autoimmune diseases, chronic inflammatory conditions, were pregnant or nursing mothers, had active infections, or were on immunosuppressive agents were excluded from the study. Only newly diagnosed patients about to receive chemotherapy were included.

Sample Collection

At Nanakali Hospital, blood samples were collected from leukemia patients at two time points: once before chemotherapy (baseline) and once after chemotherapy. We had 34 newly diagnosed

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cases of leukemia before chemotherapy and the same patients were taken after the induction phase of chemotherapy. All samples were processed in serum separator tubes they were allowed to clot, centrifuged, and then stored at -80°C until analysis. Cortisol samples were specifically taken in the morning to account for diurnal variation, and careful sample handling ensured reliable results.

Laboratory Analysis

For inflammatory marker assessment, IL-6 and TNF-α were measured using Sandwich-ELISA kits. This method involved target proteins binding to specific antibodies in microplate wells, which then reacted with HRP-conjugated antibodies and were detected through a colorimetric reaction at 450 nm. Concentrations were determined by comparing optical density against a reference curve. CRP and cortisol levels were measured using the Cobas e 411 analyzer.

Statistical Analysis

The standard error of the mean (SEM) is used to express mean values in data. "n" stands for the number of patients. Paired t-tests were used to compare biomarker levels within groups before and after chemotherapy. The threshold for statistical significance was set at $p < 0.05$. SPSS software (version 26; IBM Corp., Armonk, NY, USA) was used for all analyses.

3. RESULTS

C-Reactive Protein (CRP) Levels Before and After Chemotherapy

Post chemotherapy blood work demonstrate significant reductions in systemic CRP for both forms of leukemia (ALL and AML). In patients with ALL, mean ± SEM CRP values were 49.868±17.806 mg/L prior to chemotherapy and 1.954±1.127 mg/L after ($P = 0.004$). In patients with AML, values decreased from 60.479±14.066 mg/L to 18.05±5.81 mg/L ($P = 0.010$). These results support achievement of systemic inflammatory reduction by chemotherapy in patients with both forms of leukemia (Figure 1).

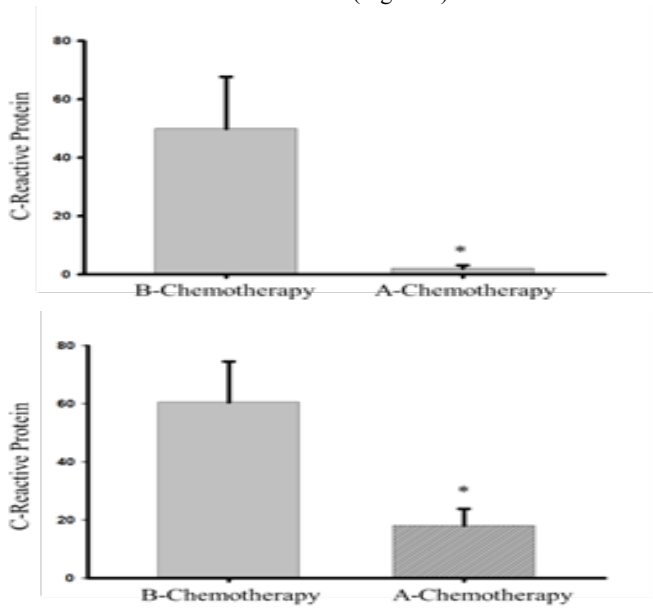


Figure 1: C-Reactive Protein (CRP) levels in blood serum of cancer patients before and after receiving chemotherapy (n = 34). **A)** Acute Lymphoblastic Leukemia (ALL) and **B)** Acute Myeloid Leukemia (AML). (Significance levels according to the paired t-test: *p =0.004 and 0.010 respectively. The vertical bars represent SEM.

Cortisol Levels Before and After Chemotherapy

Both ALL and AML patients experienced a considerable drop in cortisol levels after treatment. From 175.885±64.111 nmol/L to 49.953±27.176 nmol/L, the mean cortisol levels in ALL decreased ($P = 0.008$). A substantial mean decreases from 540.500±59.036 nmol/L to 253.642±67.047 nmol/L ($P < 0.05$) was seen for AML patients using a paired t-test. This implies that treatment reduces stress reactions in both forms of leukemia (Figure 2).

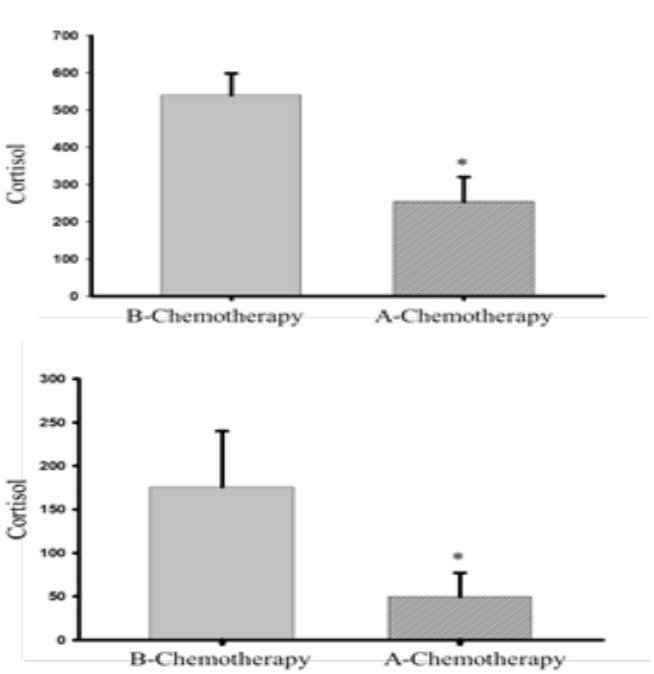
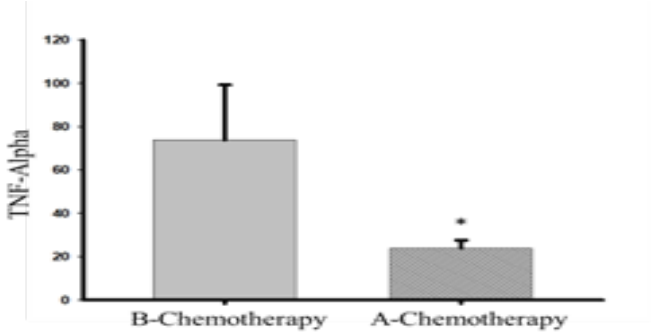


Figure 2: Cortisol levels in blood serum of cancer patients before and after receiving chemotherapy (n =34). **A)** Acute Lymphoblastic Leukemia (ALL) and **B)** Acute Myeloid Leukaemia (AML). (significance levels according to the paired t-test: *p =0.008 and <0.05. The vertical bars represent SEM.

Tumor Necrosis Factor-Alpha (TNF-α) Levels Before and After Chemotherapy

Following treatment, both ALL and AML patients reported a significant change in the Tumor Necrosis Factor-Alpha (TNF-α) levels, as it decreased considerably. From a mean of 70.822±32.103 pg/mL to 26.864±3.116 pg/mL, TNF-α levels decreased in ALL ($P = 0.008$). Likewise, TNF-α levels in AML patients decreased from 73.849±25.4 pg/mL to 23.808±3.724 pg/mL ($P = 0.007$). This suggests that chemotherapy is effectively reducing inflammatory cytokines in both forms of leukemia (Figure 3).



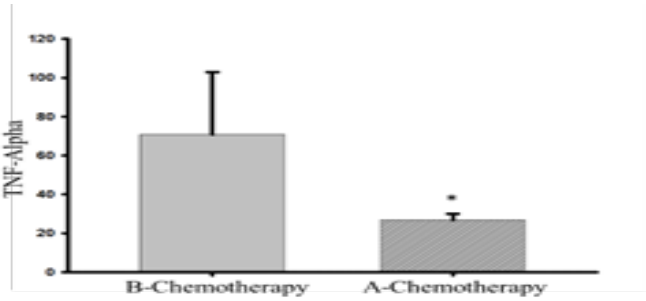


Figure 3: TNF-α levels in blood serum of cancer patients before and after receiving chemotherapy (n =34). **A)** Acute Lymphoblastic Leukemia (ALL) and **B)** Acute Myeloid Leukemia (AML). (significance levels according to the paired t-test: *p =0.008 and 0.007 respectively. The vertical bars represent SEM.

Interleukin-6 (IL-6) Levels Before and After Chemotherapy

Throughout the course of chemotherapy, both ALL and AML patients demonstrated a drop in IL-6 levels which was significant. Between 39.35±23.074 pg/mL and 11.482±0.715 pg/mL, the mean IL-6 levels in ALL dropped ($P = 0.039$). IL-6 decreased from 41.784±24.237 pg/mL to 10.724±0.731 pg/mL in AML ($P < 0.001$). The data demonstrates that chemotherapy is able to assist leukemia patients with their inflammatory response (Figure 4).

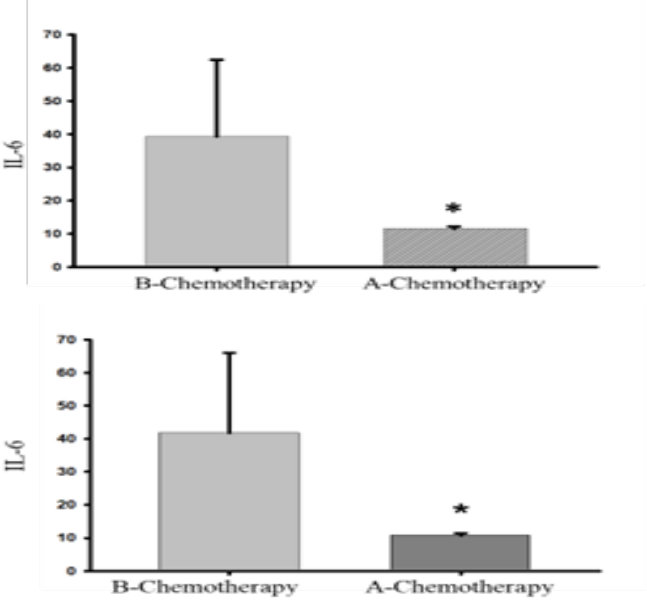


Figure 4: IL-6 levels in blood serum of cancer patients before and after receiving chemotherapy (n =34). **A)** Acute Lymphoblastic Leukemia (ALL) and **B)** Acute Myeloid Leukemia (AML). (significance levels according to the paired t-test: *p =0.039 and <0.001 respectively. The vertical bars represent SEM.

4. DISCUSSION

The outcomes indicate treatment precisely reduces stress markers and inflammation of patients suffering from AML and ALL. Diminished cortisol concentration suggests this patient group is experiencing reduced physiological stress, while lowered concentration in CRP, TNF-α, and IL-6 is an indicator of systemic inflammation reduction due to chemotherapy (Anand et al., 2023)(Baldo, 2016). This set of results consolidates previous finds that reported the role of chemotherapy in helping manage the inflammatory response commonly associated with many hematological malignancies cancerous pathways (Bruserud et al., 2020)(Burocziova et al., 2023). The degree of inflammation greatly affects the progression of leukemia as well as its responsiveness to treatment. Inflow in the levels of CRP, TNF-α and IL-6 concentration in leukemic patients is linked to worsened disease prognosis hence more advanced stages of ailing to incurable leukemia (Flaherty et al., 2019)(Hu et al., 2024). It is possible that chemotherapy improves outcome by relieving the inflammatory burden as witnessed by the significant drop in several markers post-chemotherapy. Moreover, the decrease of cortisol observed is a positive sign as it suggests chemotherapy relieves physiological stress which is vital bearing in mind that stress and hormones tend to influence treatment effectiveness and immune response (Kareva, 2017)(Krsek et al., 2024). For some reason, the baseline CRP inflammation marker was greater for AML patients when compared to ALL patients, which might hint towards a worse inflammatory state. This suggests that inflammation plays a greater role in the pathophysiology of AML, which may explain why there was a more dramatic reduction in CRP following treatment with therapy agnostic to the type of cancer in the AML patients. The gradual reduction in pro-inflammatory mediators TNF-α and IL-6 for both types of leukemia illustrates the impact of chemotherapy on cytokine moderation, verifying its role in inflammation alleviation associated with leukemia (Flaherty et al., 2019)(Kareva, 2017)(Morrow et al., 2002). Apart from the metabolic changes, the possible therapeutic consequences represent another major aspect of this study. These changes may improve survival outcomes while reducing the risk of complications such as infections or treatment-related toxicity due to lower levels of inflammation and stress responses. Future research is needed to determine if these biochemical changes bring about enhanced quality of life and remission rates, among other clinically relevant issues in the long term (Bruserud et al., 2020)(Mukherjee et al., 2023). Moreover, even when chemo works towards achieving some negative inflammation and stress indicators, it still has immunosuppressive effects and other damaging consequences. Hence, it becomes necessary to research adjunct therapies that can reduce the negative impacts of chemotherapy while maximizing its positive results. It may be beneficial to combine the procedures used for treating leukemia with the administration of anti-inflammatory medication, nutritional therapy, and relaxation techniques (Anand et al., 2023)(Saadi et al., 2021). Considering all of these factors, these outcomes explain the ways in which chemotherapy aids patients suffering from leukemia in terms of their inflammatory and stress markers. For a more comprehensive understanding of the relationship between biochemical processes and clinical changes, future efforts need to focus on larger cohorts with longer follow-up periods. Targeting inflammation concurrently with the use of chemotherapy might improve patient and therapeutic outcomes overall (Bruserud et al., 2020)(Sproston & Ashworth, 2018).

CONCLUSIONS

This investigation reveals chemotherapy's multifaceted impact in acute leukemias, showing significant reductions in pro-inflammatory mediators (CRP, TNF-α, IL-6) and hypothalamic-pituitary-adrenal axis activation (cortisol). The coordinated decline of these biomarkers provides mechanistic evidence for chemotherapy's capacity to modulate both inflammatory pathways and stress physiology in AML/ALL. These biochemical improvements correlate with clinical recovery patterns, suggesting that conventional chemotherapy regimens may inherently regulate immune-stress crosstalk during leukemia treatment. The parallel responses observed across distinct leukemia subtypes further underscore the fundamental biological effects of cytotoxic therapy on systemic homeostasis.

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Ethical statement

The study was approved by the Ethics Committee of Health Sciences College, Hawler Medical University University. (Approval No. Sc.E.C.11B2).

Author contributions

C.Y.A. conceived and designed the study, collected the data, performed the analysis, and drafted the manuscript. R.A.H. contributed to the study design, data interpretation, and critical revision of the manuscript. All authors have read and agreed to the published version of the manuscript.

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