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COMPARATIVE OUTCOMES OF HYPER-CVAD VERSUS UKALL PROTOCOLS IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN ADOLESCENTS AND ADULTS

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is a heterogeneous hematological malignancy requiring intensive chemotherapy. In Iraq, ALL represents the most common hematological malignancy, contributing to 41% of all leukemia cases. Limited comparative data exist on the outcomes of different protocols in Iraqi patient populations. **Objective:** To evaluate and compare the clinical outcomes of two chemotherapy regimens—Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and UKALL (United Kingdom Acute Lymphoblastic Leukemia)—in adult patients with newly diagnosed ALL at Baghdad Teaching Hospital. **Patients and Methods:** This prospective study was conducted from January 2017 to December 2018 and included 60 patients aged ≥14 years with newly diagnosed ALL. Patients were treated with either the UKALL protocol (n=31) or the Hyper-CVAD protocol (n=29) based on clinical judgment. Follow-up assessments included complete remission rate at two months (CR2M), overall complete remission (CR), relapse rate, and mortality. Statistical analysis was performed using SPSS version 25, with survival analysis conducted via the Kaplan-Meier method. **Results:** The cohort comprised 60 patients (58.3% male) with a mean age of 27.83 ± 14.22 years. B-ALL was diagnosed in 70% (n=42) and T-ALL in 30% (n=18). Philadelphia chromosome positivity was 18.3% (n=11). The Hyper-CVAD protocol demonstrated a significantly higher CR2M rate compared to UKALL (93.1% vs. 67.7%, P=0.014). Overall CR was 89.6% for Hyper-CVAD versus 48.4% for UKALL. Relapse and mortality rates were lower in the Hyper-CVAD group (6.9% and 10.3%, respectively) compared to the UKALL group (16.1% and 19.4%, respectively). In the B-ALL subgroup, Hyper-CVAD achieved an 85.7% CR versus 42.8% with UKALL. In the T-ALL subgroup, Hyper-CVAD achieved a 100% CR versus 60% with UKALL. No statistically significant difference was found between the two protocols in terms of overall survival (OS) (P=0.963). **Conclusion:** The Hyper-CVAD protocol was associated with significantly higher early and overall complete remission rates compared to the UKALL protocol in this patient cohort. However, this improvement in remission did not translate into a statistically significant difference in overall survival, underscoring the need for longer follow-up and consideration of post-remission strategies like transplantation.

KEYWORDS: Acute lymphoblastic leukemia, chemotherapy protocols, complete remission, Hyper-CVAD, UKALL, overall survival.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic neoplasm characterized by the clonal proliferation and accumulation of immature lymphoid cells in the bone marrow, peripheral blood, and extramedullary sites.[2] The age-adjusted incidence rate of ALL in the United States is approximately 1.58 per 100,000 individuals per year, with an estimated 6,500 new cases diagnosed in 2024.[9] The median age at diagnosis is 15 years, with 57.2% of patients diagnosed before the age of 20.[2]

Over recent decades, cure rates and survival outcomes for patients with ALL have improved dramatically, particularly in the pediatric population. These advancements are largely attributed to an improved understanding of molecular genetics, the implementation of risk-adapted therapy, the development of targeted agents, and the strategic use of allogeneic hematopoietic cell transplantation (HCT).[3] However, outcomes for adults remain inferior, with 5-year overall survival (OS) rates of 24.1% for patients aged 40-59 years and 17.7% for those aged 60-69 years.[2]

Several intensive chemotherapy regimens are standard in ALL management, including the UKALL protocol, developed by the Medical Research Council (MRC) in the UK, and the hyper-CVAD regimen, developed at the MD Anderson Cancer Center. The UKALL protocol, evaluated in large trials including UKALL 2003 and UKALL 2011, consists of induction therapy with vincristine, daunorubicin, prednisone/dexamethasone, and L-asparaginase, followed by consolidation and maintenance phases.[3] The hyper-CVAD regimen comprises eight alternating treatment cycles: cycle A with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with cycle B, which includes high-dose methotrexate and cytarabine.[2]

While international studies have reported outcomes for these protocols individually, prospective comparative data, particularly from Iraqi populations, are limited. In Iraq, ALL represents a significant burden, accounting for 41% of all leukemia cases.[1] A recent 17-year experience from a Baghdad pediatric center demonstrated that while survival rates have progressively improved, they remain below those observed in high-income countries, with toxic deaths representing an important cause of treatment failure.[7] This study was designed to prospectively evaluate and compare the efficacy and tolerability of the Hyper-CVAD and UKALL protocols in adult and adolescent patients with ALL at a single tertiary care center in Baghdad, with respect to remission rates, relapse, and mortality.

PATIENTS AND METHODS

Ethical Approval: The study was approved by the Institutional Review Board of Baghdad Teaching Hospital / Medical City. Written informed consent was obtained from all patients or their legal guardians in accordance with the Declaration of Helsinki.

Study Design and Population: This prospective, comparative study was conducted from January 2017 to December 2018 at the Hematology Unit, Baghdad Teaching Hospital / Medical City. A total of 60 patients, aged 14 years and older, with newly diagnosed ALL were enrolled. Diagnosis was confirmed by bone marrow morphology and flow cytometry. All patients were eligible for and received intensive chemotherapy.

Diagnostic Evaluation: diagnosis was established based on.

1. **Morphology:** Examination of Wright-Giemsa-stained bone marrow aspirate and peripheral blood smears.
2. **Immunophenotyping:** Comprehensive flow cytometry performed on peripheral blood or bone marrow aspirate to confirm lineage (B-ALL or T-ALL).
3. **Cytogenetics:** Fluorescence in situ hybridization (FISH) analysis to detect the Philadelphia chromosome (t (9;22)).

Treatment Protocols: The treatment protocol (Hyper-CVAD or UKALL) was selected by the treating physician based on clinical judgment, patient age, and protocol availability at the time.

- **UKALL Protocol:** Patients received a risk-adapted UKALL regimen based on protocols established in UKALL trials.[3] Those aged 14-25 years were treated according to pediatric-inspired protocols, while patients >25 years received adapted UKALL regimens. In brief, this involved two phases of induction, followed by consolidation blocks (including high-dose methotrexate), delayed intensification phases, interim maintenance, and a two-year maintenance phase.
- **Hyper-CVAD Protocol:** This dose-intensive regimen consisted of up to eight cycles, alternating between Course A and Course B, with prophylactic intrathecal chemotherapy and granulocyte colony-stimulating factor (G-CSF) support (Course A: Cyclophosphamide, vincristine, doxorubicin, and dexamethasone; Course B: High-dose methotrexate and cytarabine).[2]
- **Philadelphia Chromosome-Positive (Ph+) Patients:** All patients with confirmed Ph+ ALL received the tyrosine kinase inhibitor Imatinib at a dose of 400 mg daily in addition to their assigned chemotherapy protocol, consistent with current approaches incorporating TKIs with multiagent chemotherapy.[9]

Supportive Care

Standardized supportive care was provided to all patients. This included prophylactic and therapeutic transfusions of packed red blood cells (to maintain hemoglobin >7 g/dL) and platelets (for counts <20 ×

10^9/L or active bleeding). Broad-spectrum antibiotics were administered for febrile neutropenia or documented infections. Prophylaxis for tumor lysis syndrome (allopurinol, hydration) and antifungal, antiviral, and *Pneumocystis jirovecii* pneumonia prophylaxis were administered according to institutional guidelines. Pre-treatment evaluations included electrocardiography, echocardiography, virology screening, abdominal ultrasound, and chest X-ray.

Response Assessment

- **Complete Remission at Two Months (CR2M):** Assessed by bone marrow aspirate performed two months after treatment initiation.
- **Overall Complete Remission (CR):** Defined as <5% blasts in a normocellular bone marrow, an absolute neutrophil count >1.0 × 10^9/L, and a platelet count >100 × 10^9/L. Response was assessed post-induction (for UKALL) or after the first cycle (for Hyper-CVAD).
- **Relapse:** Defined as the recurrence of >5% lymphoblasts in the bone marrow or the appearance of extramedullary disease after achieving CR.
- **Overall Survival (OS):** Calculated from the date of diagnosis to the date of death from any cause or last follow-up.

Statistical Analysis

Data were analyzed using SPSS version 25. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means and standard deviations. An independent samples t-test was used to compare means between the two protocol groups. The Kaplan-Meier method with the log-rank test was used to estimate and compare overall survival. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Patient Demographics and Baseline Characteristics

The study included 60 patients with a mean age of 27.83 ± 14.22 years. The majority were male (n=35, 58.3%). The most frequent clinical presentations were pallor (91.7%) and fever (90.0%). Table 1 summarizes the baseline characteristics of the study cohort.

Table 1: Baseline Demographics and Clinical Characteristics of Patients (n=60)

Characteristic	Category	Frequency (n)	Percentage (%)
Gender	Male	35	58.3%
	Female	25	41.7%
Age Group	14-25 years	38	63.3%
	26-65 years	21	35.0%
	>65 years	1	1.7%
Immunophenotype	B-ALL	42	70.0%
	T-ALL	18	30.0%
Philadelphia Chromosome	Positive	11	18.3%
	Negative	49	81.7%
Common Presentations	Pallor	55	91.7%
	Fever	54	90.0%
	Lymphadenopathy	31	51.7%
	Splenomegaly	29	48.3%

Protocol Distribution and Comparability

Of the 60 patients, 29 (48.3%) received Hyper-CVAD, and 31 (51.7%) received the UKALL protocol. As shown in Table 2, there was no statistically significant association between the type of protocol received and the patient's age group (P=0.528), confirming the comparability of the two arms in terms of age distribution.

Table 2: Association Between Age Group and Type of Protocol.

Age Group	Hyper-CVAD (n=29)	UKALL (n=31)	Total (N=60)	*P*-value
14-25 years	18 (47.4%)	20 (52.6%)	38	0.528
26-65 years	11 (52.4%)	10 (47.6%)	21	
>65 years	0 (0.0%)	1 (100%)	1	

Furthermore, no significant differences were observed between the two protocol groups regarding mean age or mean presenting white blood cell (WBC) count, as detailed in Table 3, indicating that the groups were well-balanced for these key prognostic factors.

Table 3: Comparison of Mean Age and WBC Count Between Protocol Groups.

Variable	Hyper-CVAD (n=29)	UKALL (n=31)	*P*-value
Mean Age (years)	26.9 ± 13.5	28.7 ± 14.8	0.993
Mean WBC Count (×10^9/L)	68.0	65.0	0.382

Treatment Outcomes

Table 4 presents a comprehensive comparison of treatment outcomes between the two protocols. The Hyper-CVAD regimen was associated with a significantly higher rate of complete remission at two months (CR2M) compared to the UKALL protocol (93.1% vs. 67.7%, P=0.014). This superior early response translated into a markedly higher overall complete remission rate for Hyper-CVAD (89.6%) compared to UKALL (48.4%). Correspondingly, relapse and mortality rates were lower in the Hyper-CVAD group.

Table 4: Comparison of Treatment Outcomes by Protocol.

Outcome	Hyper-CVAD (n=29)	UKALL (n=31)	*P*-value
CR at 2 Months (CR2M)	27 (93.1%)	21 (67.7%)	0.014
Overall Complete Remission (CR)	26 (89.6%)	15 (48.4%)	0.001
Relapse	2 (6.9%)	5 (16.1%)	0.25
Deaths	3 (10.3%)	6 (19.4%)	0.32

Figure 1 illustrates the final outcomes for the entire study cohort, showing that 68.3% of patients achieved complete remission by the end of the study period.

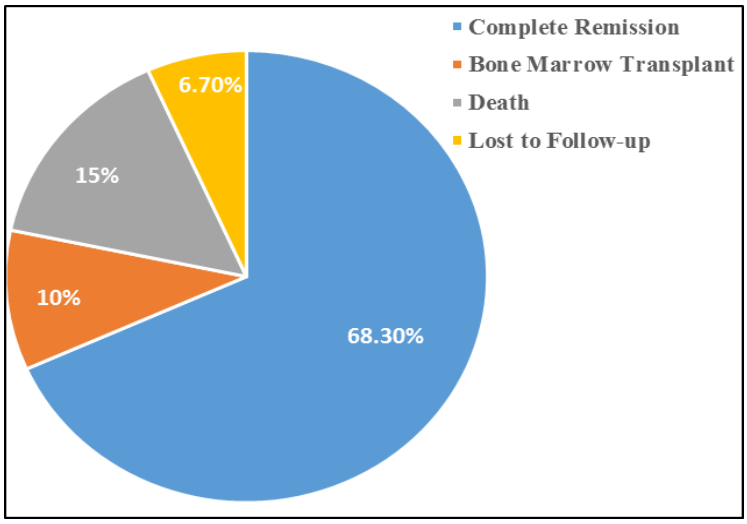

Figure 1: Final Outcomes of the Study Cohort (N=60).

Subgroup Analysis by Immunophenotype

Outcomes were analyzed according to ALL subtype. In both B-ALL and T-ALL subgroups, patients treated with Hyper-CVAD demonstrated superior CR rates and lower relapse/mortality compared to those treated with UKALL, as depicted in Figure 2. Notably, the Hyper-CVAD protocol achieved a 100% CR rate with no deaths in the small T-ALL subgroup.

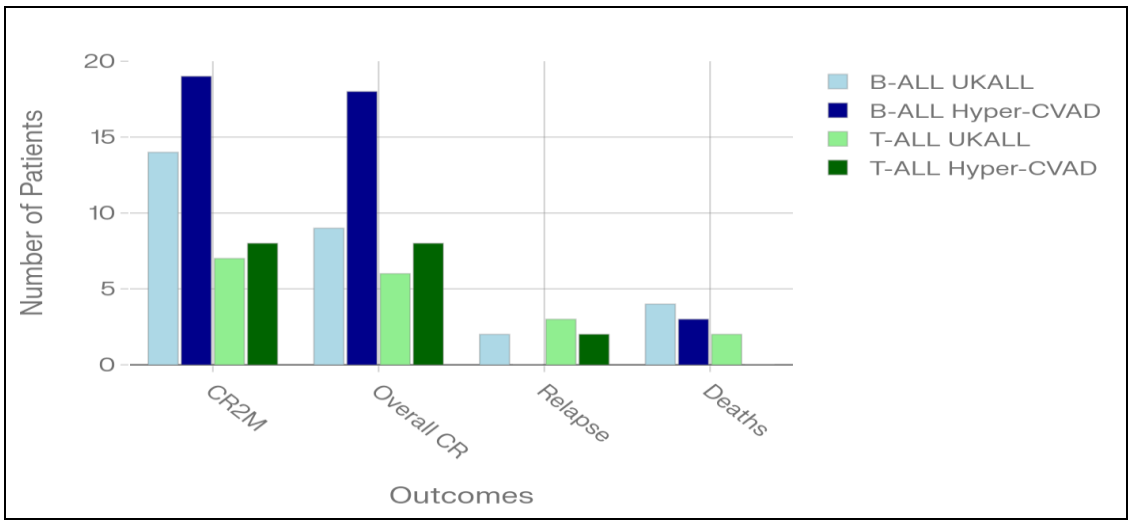

Figure 2: Treatment Outcomes by ALL Subtype and Protocol.

Survival Analysis

Kaplan-Meier analysis was performed to assess overall survival. Despite the significant differences in remission rates, the log-rank test revealed no statistically significant association between the type of protocol received and overall survival (P=0.963). The survival curves for the two protocols were nearly superimposable.

DISCUSSION

This prospective study provides valuable real-world data on the outcomes of two common chemotherapy regimens for ALL in an Iraqi population. The demographic profile, with a male predominance and a mean age of 27.8 years, is consistent with findings from other studies in the region and internationally.[1,7] The immunophenotypic distribution (70% B-ALL, 30% T-ALL) and Philadelphia chromosome positivity rate (18.3%) also align with published literature, where B-ALL accounts for approximately 75% of cases and Ph+ ALL occurs in 10-25% of adults.[9]

The most clinically significant finding of this study is the markedly superior complete remission rate achieved with the Hyper-CVAD protocol. The CR2M rate of 93.1% with Hyper-CVAD was significantly higher than the 67.7% observed with the UKALL protocol (P=0.014). This advantage persisted in the overall CR rate (89.6% vs. 48.4%) and across both B-ALL and T-ALL subgroups. The CR rate for Hyper-CVAD in our study (89.6%) is comparable to the 88% composite complete response rate reported by Mohamed et al. in a Cleveland Clinic study[2] and the 89.6% overall CR rate reported by Çiftçiler *et al*. in a Turkish multicenter study, suggesting that this regimen is feasible and effective in similar regional contexts.[1]

In contrast, the overall CR rate for the UKALL protocol in our cohort (48.4%) was considerably lower than the 86% complete remission rate reported in the Iraqi pediatric experience with modified UKALL protocols at Children's Welfare Teaching Hospital[7] and the 85% reported in the large MRC UKALL trials.[3] This significant discrepancy warrants careful consideration and highlights the challenges of translating clinical trial results into real-world practice, particularly in resource-limited settings. Several factors may have contributed to the lower-than-expected efficacy of the UKALL protocol in our study.

1. **Treatment Adherence and Compliance:** The UKALL protocol requires more frequent and prolonged hospital admissions. Clinical observation suggested that this led to higher rates of patient non-compliance and early treatment discontinuation, which can profoundly impact outcomes. In the Iraqi pediatric experience, treatment abandonment occurred in 13% of cases, representing a significant cause of treatment failure.[7]
2. **Toxicity and Dose Modifications:** L-asparaginase, a critical component of the UKALL regimen, is associated with significant toxicities, including thromboembolic events and hepatotoxicity. In our study, two patients on the UKALL protocol developed such events, necessitating the omission of this key drug and potentially compromising the protocol's effectiveness. The Iraqi pediatric experience identified toxic deaths as an important cause of failure, occurring in 8% of patients.[7]
3. **Supportive Care Infrastructure:** The management of intensive regimens like UKALL requires robust supportive care to manage myelosuppression and infectious complications. Challenges in this area may have contributed to higher infection-related mortality and morbidity, as reflected in the higher death rate (19.4% vs. 10.3%) in the UKALL group. Studies from other developing countries have similarly identified limitations of treatment intensification in resource-constrained settings.[8]
4. **Age and Protocol Appropriateness:** The UKALL 2011 trial, which included patients younger than 25 years, demonstrated good outcomes with 5-year CNS relapse rates of approximately 5%.[3] However, our cohort included patients up to 65 years, and the adaptation of pediatric-inspired regimens for older adults may be associated with increased toxicity and reduced efficacy.

Despite the superior remission rates with Hyper-CVAD, the study found no significant difference in overall survival between the two groups (P=0.963). This seemingly paradoxical finding is not uncommon in oncology trials, where improvements in early response do not always translate into long-term survival benefits. OS is a composite endpoint influenced by many factors beyond initial remission, including the success of post-remission consolidation, the ability to proceed to allogeneic HCT in eligible patients, and the effective management of relapsed disease. The short follow-up period of this study may also have been insufficient to capture a survival difference, as late relapses and long-term toxicities can impact OS over a longer horizon. The low rate of allogeneic HCT (only 10% of the cohort) in our study may also have blunted any potential survival advantage from the initial higher-quality remission achieved with Hyper-CVAD, consistent with observations that allogeneic HCT consolidation improves leukemia-free survival in responding patients.[5]

Recent comparative studies have yielded variable results regarding the relative efficacy of different regimens. Mohamed et al. found that Hyper-CVAD was associated with higher flow cytometry-minimal residual disease negative responses compared to the CALGB-19802 regimen (an asparaginase-utilizing regimen), with 3-year OS of 71% for Hyper-CVAD versus 49% for CALGB-19802 (P=0.14).[2] Conversely, Zalapa-Soto et al. demonstrated superior outcomes with a modified pediatric-inspired regimen (mCALGB) compared to Hyper-CVAD in Hispanic patients, with 3-year OS of 64.9% versus 34.9% (P=0.034).[10] A meta-analysis by Su

et al. suggested that patients receiving pediatric-inspired regimens were approximately twice as likely to achieve a complete response and 1.8 times more likely to survive than patients receiving Hyper-CVAD.[6] These contrasting findings underscore the importance of patient population, treatment setting, and supportive care infrastructure in determining optimal protocol selection.

The higher early mortality rate in the UKALL group (19.4% vs. 10.3%) is concerning and warrants further investigation. In the Iraqi pediatric experience, early deaths occurred in 10% of children, decreasing to 6% in the most recent treatment period (2012-2016).[7] The higher rate in our adult cohort may reflect increased vulnerability of adult patients to treatment-related toxicities, particularly infectious complications during prolonged neutropenia. Jain et al., in a study from a developing country, similarly found that intensified therapy in high-risk ALL was associated with a significant increase in early treatment-related mortality and cost, without a clear survival benefit.[8]

The excellent outcomes in the T-ALL subgroup treated with Hyper-CVAD (100% CR, no deaths) are noteworthy, though the small sample size (n=18) limits definitive conclusions. Current approaches to T-ALL incorporate combination chemotherapy regimens with pegylated asparaginase and nelarabine, and early T-cell precursor ALL is a high-risk subgroup for which allogeneic SCT should be considered.[9]

Limitations

This study has several limitations that must be acknowledged when interpreting its findings. The relatively small sample size (n=60) limits the statistical power for subgroup analyses and survival comparisons. As a single-center study, the findings may not be fully generalizable to other institutions with different patient populations and resources. The non-randomized assignment of protocols introduces the potential for selection bias. Furthermore, the absence of minimal residual disease (MRD) testing, a now-critical prognostic tool for guiding therapy and predicting relapse, is a significant limitation. MRD negativity is increasingly recognized as an important prognostic indicator that may identify patients who could avoid allogeneic stem cell transplantation. The short follow-up period precludes definitive conclusions about long-term outcomes such as 5-year OS and late relapse.

Despite these limitations, this study provides important, real-world evidence from a previously underreported population and offers critical insights for clinicians managing ALL in similar settings.

CONCLUSIONS

1. **Superior Remission Rates with Hyper-CVAD:** In this prospective study, the Hyper-CVAD protocol was associated with significantly higher rates of both early and overall complete remission compared to the UKALL protocol in adult and adolescent patients with newly diagnosed ALL.
2. **Favorable Short-Term Outcomes:** Patients treated with Hyper-CVAD experienced lower relapse and mortality rates, particularly in the T-ALL subgroup, where outcomes were excellent.
3. **Discrepancy with Long-Term Survival:** The significant improvement in remission did not translate into a statistically significant difference in overall survival, likely due to the influence of post-remission factors, the short follow-up period, and the small sample size.
4. **Challenges with the UKALL Protocol:** The lower efficacy of the UKALL protocol in this setting may be related to higher rates of toxicity, treatment discontinuation, and challenges in delivering the complex regimen with optimal supportive care.
5. **Independent of Traditional Risk Factors:** The superior performance of Hyper-CVAD was observed irrespective of age and presenting WBC count.

RECOMMENDATIONS

1. **Long-term Follow-up:** Extended follow-up of this cohort is essential to determine whether the superior remission rates with Hyper-CVAD ultimately lead to an improvement in long-term overall survival.
2. **Risk-Adapted Protocol Selection:** In clinical settings with limited resources and challenges in delivering complex, prolonged regimens, Hyper-CVAD may be a preferred first-line option for adult ALL, especially for achieving rapid disease control and in patients with T-ALL.
3. **Strengthen Supportive Care:** Improving supportive care infrastructure, including infection control, transfusion support, and management of regimen-specific toxicities (like L-asparaginase-associated thromboembolism), is critical for optimizing outcomes with either protocol, particularly UKALL.
4. **Enhance Treatment Adherence:** Developing patient support programs, including education, social work, and financial assistance, is crucial to improve adherence to demanding treatment protocols like UKALL.
5. **Incorporate MRD Testing:** Establishing routine minimal residual disease (MRD) monitoring is paramount. MRD status is the single most powerful prognostic factor and should guide post-remission therapy, including decisions about allogeneic HCT.
6. **Expand Transplant Access:** Efforts should be made to increase the availability of allogeneic hematopoietic cell transplantation for high-risk patients who achieve first remission, as this remains the most effective strategy for preventing relapse and improving long-term survival.
7. **Establish Multicenter Collaboration:** Creating a national ALL registry and fostering collaboration between Iraqi centers will be vital for generating larger datasets, conducting more robust research,

and ultimately developing evidence-based guidelines tailored to the Iraqi population.

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