Prognostic significance of CD20 expression in Adults B-cell acute lymphoblastic leukemia

Importancia pronóstica de la expresión de CD20 en leucemia linfoblástica aguda de células B en adultos

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Abstract

Introduction: Acute lymphoblastic leukemia is a lymphocyte malignancy characterized by clonal buildup of immature blood cells in the bone marrow that are halted in the lymphoblast stage of development. CD20 is expressed on both normal and malignant B-cell lineage cells at all stages of development except precursor and plasma cells in 40-60% of B-cell precursor ALL patients. The aim of study is to evaluate CD20-positive B-ALL patients and comparing post-induction complete remission, event-free survival, and overall survival between those who received rituximab and those who did not. **Method:** Retrospective, prospective single-center cohort research at Baghdad Hematology Teaching Centre, Medical Complex, Iraq. Forty-nine Iraqi B-ALL patients from January 2017 to August 2021 were studied. The laboratory teaching centre and participants gather data during their frequent trips to the hospital's ward, day care unit, and consultation room. **Results:** At diagnosis, patients were (33.5±17.9) years old and 1.8:1 male to female. All patients had CD20 expression, with 48.98% diverse and 12.24% moderate. Significant connection. Rituximab-treated individuals survived 50% in the first year, 45% in the second, and 5% in the third. Overall survival is significantly different between patients who got rituximab with induction regimen and those who did not (P= 0.049). Male gender is associated with overall survival. WBC, age, Philadelphia chromosome positive, and expressions did not affect overall survival between the two groups. Rituximab did not affect event-free survival (P=0.2). Event-free survival (EFS=36 months) is significantly higher in R-hyper CVAD patients. **Conclusion:** Rituximab improved survival. Male gender affects survival. Rituximab did not improve event-free survival.

Keywords: Prognostic, significance, CD20 expression, Adults, B-cell, acute lymphoblastic leukemia.

Resumen

Introducción: La leucemia linfoblástica aguda es una neoplasia maligna de linfocitos caracterizada por la acumulación clonal de células sanguíneas inmaduras en la médula ósea que se detienen en la etapa de desarrollo de linfoblastos. CD20 se expresa en células de linaje de células B tanto normales como malignas en todas las etapas de desarrollo, excepto en células precursoras y plasmáticas en el 40-60 % de los pacientes con LLA de precursores de células B. El objetivo del estudio es evaluar a los pacientes con B-ALL positivos para CD20 y comparar la remisión completa posterior a la inducción, la supervivencia libre de eventos y la supervivencia general entre los que recibieron rituximab y los que no. **Método**: investigación retrospectiva prospectiva de cohorte de un solo centro en el Centro de Enseñanza de Hematología de Bagdad, Complejo Médico, Irak. Se estudiaron cuarenta y nueve pacientes iraquíes con B-ALL desde enero de 2017 hasta agosto de 2021. El centro de enseñanza del laboratorio y los participantes recopilan datos durante sus frecuentes viajes a la sala del hospital, la unidad de cuidado diurno y la sala de consulta. **Resultados**: Al momento del diagnóstico, los pacientes tenían (33,5±17,9) años y 1,8:1 de hombres a mujeres. Todos los pacientes tenían expresión de CD20, con un 48,98% diversa y un 12,24% moderada. Conexión significativa. Los individuos tratados con rituximab sobrevivieron un 50 % en el primer año, un 45 % en el segundo y un 5 % en el tercero. La supervivencia global es significativamente diferente entre los pacientes que recibieron rituximab con el régimen de inducción y los que no lo recibieron (p = 0,049). El sexo masculino se asocia con la supervivencia global. WBC, la edad, el cromosoma Filadelfia positivo y las expresiones no afectaron la supervivencia general entre los dos grupos. Rituximab no afectó la supervivencia libre de eventos (P = 0,2). La supervivencia libre de eventos

(SSC = 36 meses) es significativamente mayor en los pacientes con R-hiper CVAD. **Conclusión**: Rituximab mejoró la supervivencia. El género masculino afecta la supervivencia. Rituximab no mejoró la supervivencia libre de eventos.

Palabras clave: pronóstico, significado, expresión de CD20, adultos, células B, leucemia linfoblástica aguda.

transplantation is an effective treatment option[19]. The aim of study is to assess the outcome of patients with CD20 positive B-ALL and Comparing the outcome of patients who received rituximab with patients who did not receive rituximab in terms of first complete remission, event free survival and overall survival.

Introduction

Acute lymphoblastic leukemia (ALL) is a malignancy of lymphocytes characterized by immature blood cells accumulation in the bone marrow[1,2]. It is most prevalent in children, representing 76% of pediatric leukemia cases, but also occurs in adults[3-5]. Diagnosis involves identifying marrow failure, extra medullary disease[6], and leukemic blasts in cerebrospinal fluid[3,4]. Classification now uses WHO standards which consider cytogenetics, immunophenotyping, and molecular information[4,5]. Age, initial WBC count, and immunophenotype are critical predictors of event-free survival and overall survival[7]. CD20, a B-cell lineage-specific antigen, is vital for cell-cycle progression, differentiation, apoptosis pathways, and drug resistance mechanisms[8]. CD20 positive B-ALL has worse outcomes, lower remission rates, and higher relapse rates[8,9]. Rituximab, an immunotherapy agent, is used alongside standard chemotherapy to reduce relapse incidence and improve survival[10]. Other anti-CD20 antibodies such as obinutuzumab and of atumumab might offer better results for patients with low CD20 expression[10]. A study suggests that combining ofatumumab with hyper-CVAD regimen is safe and potentially provides superior outcomes[11,12]. Treatment for ALL requires managing metabolic and infectious complications, pain, and psychological support[2]. Patients diagnosed with Philadelphia chromosome positive (Ph+ve) ALL are treated with tyrosine kinase inhibitors (TKIs) alongside chemotherapy[13]. Recent suggestions propose a chemotherapy-free induction with dasatinib, followed by consolidation with blinatumumab, for first-line treatment of Ph+ve ALL due to better molecular response and reduced toxicity[14]. Refractory or relapsed disease presents a challenge, with conventional chemotherapy offering limited activity[15]. However, the introduction of novel targeting therapies, including monoclonal antibodies and CAR-T cells, has improved patient outcomes[16]. In particular, the MOpAD regimen combined with rituximab has shown promise in refractory patients with CD20 positive B-ALL[17]. Other recommended regimens include Blinatumumab, inotuzumab ozogamcin, and tisagenlecleucel[18]. For patients who fail to achieve remission after induction, relapse, or are high-risk after first complete remission, allogeneic bone marrow

Methods

This is a single center analytic cross-sectional study, both retrospective and prospective, conducted at the Baghdad Hematology Teaching Center, Iraq. The study incorporated 49 Iraqi patients diagnosed with B-acute lymphoblastic leukemia (B-ALL) from January 2017 to August 2021. Data was collected from the laboratory teaching center and directly from patients during their regular hospital visits. The inclusion criteria incorporated patients aged 15 years and above, with de novo B-ALL and CD20 positive expression detected by 8-color flow cytometry. CD20 positivity was defined as baseline CD20 expression level above 20% of leukemic cells[10]. Patients with Pro-B-ALL, Common ALL, Pre-B-ALL were included, and both Philadelphia chromosome negative and positive patients were considered. Treatment involved hyper-CVAD or UKALL regimens, based on age, performance status, comorbidities, and overall patient condition. Rituximab was added to these regimens, and tyrosine kinase inhibitors (Imatinib, Nilotinib) were used for Philadelphia chromosome positive (Ph+ve) patients. Exclusion criteria included patients with Mature B-cell (Burkitt lymphoma), negative CD20 expression, aged below 15 years, chronic myeloid leukemia in lymphoid blastic transformation, and patients with incomplete information. Outcome definitions included complete remission, defined by specific bone marrow blast, neutrophil count, platelets, and absence of extramedullary disease; relapse, denoting medullary or extramedullary recurrence of disease after achieving complete remission[2]; event-free survival, representing the time from diagnosis till treatment failure, relapse or death[8]; and overall survival, defined as the time from diagnosis until death or the end of the study[8]. The study received ethical approval and permission from The Iraqi Scientific Council of Hematology. Participants were informed about the study's purpose and gave verbal consent. Confidentiality of the information was maintained. Data was analyzed using the statistical package for social sciences (SPSS) software version 23. Descriptive statistics for socio-demographic characteristics were represented using means, standard deviation, min, max values for continuous data, and numbers and percentage values for countable data. Cox regression was used to calculate overall survival. A p-value < 0.05 indicated statistical significance.

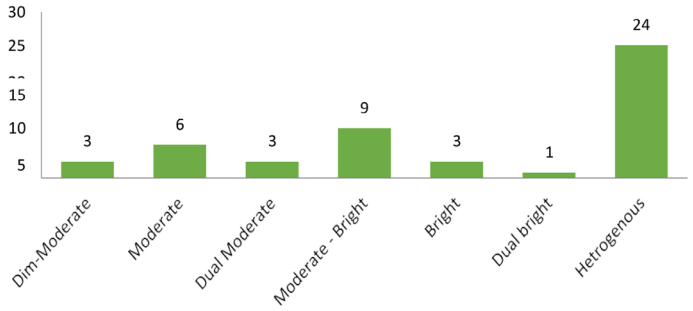
Analytic cross sectional study of 49 patients, mean age of the patients at time of diagnosis (33.5 ± 17.9) years old, minemum age presentation was 15 years old, while 75 years was the maximum. Male gender acounts 32(65.3%) of patients, while 17(34.7%) were of female gender. Male to female ratio was 1.88:1. Adolescents and young adults (AYAs) with age group of (15-39) years acounts 32 (65.3%) of patients in this study. Antigen expressions that affect the prognosis of B-ALL such as CALLA (CD10 expression) detected in 44(89.8%) of the patients and aberrant expressions (CD7, CD13 and CD33) in 7(14.3%) of the patients. Philadelphia chromosome was positive in 5(10.2%). Of the total 49 patients 27(55.1%) received Rituximab as a part of induction regimen, 22(44.9%) did not receive Rituximab or they died before starting treatment (4 patients). Of 27 patients who received Rituximab 18 of them received hyper-CVAD as induction regimen, while 9 patients received UKALL regimen, as showed in table 1.

Table 1: Patients characteristics in current study.

variables		frequency	percentage
Gender	*female*	17	34.7
	male	32	65.3
Age groups	*15-39*	32	65.3
	40-75	17	34.7
CD10 expression	*negative*	5	10.2
	positive	44	89.8
Aberrant expressions (CD7,CD13,CD33)	*no*	42	85.7
	yes	7	14.3
Philadelphia chromosome	*negative*	37	75.5
	positive	5	10.2
	unknown	7	14.3
Rituximab	*no*	22	44.9
	yes	27	55.1
Rituximab with	*hyperCVAD*	18	66.6
	UKALL	9	33.3

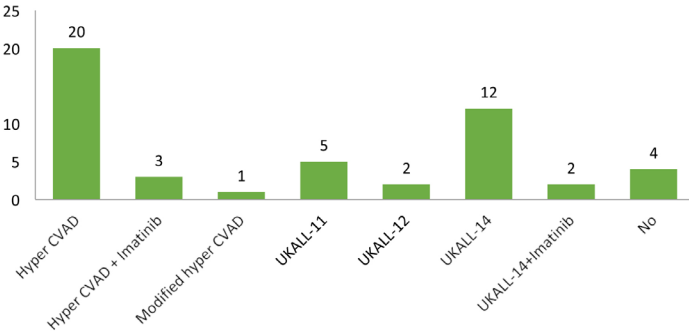
As shown in fig 1, 24(48.98%) of patients with heterogeneous CD20 expression, 6(12.24%) of them with moderate and 9(20.3%) moderate to bright.

Fig 1: pattern of CD20 expression by flowcytometry.



As shown in Fig 2, the distribution of patients according to first induction regimen, 24(48.98%) of patients treated with hyper-CVAD, 21(42.85%) were treated with pediatric inspired protocol, while 4(8.16%) had no treatment as they died before starting treatment.

Fig 2: Distribution of patients according to first induction protocol regardless to Rituximab.



According to fig 3, Overall survival, there is significant difference in overall survival between patients who receive rituximab with induction regimen and patients who did not.

Fig 3: Overall survival of patients with or without receiving Rituximab. OS (P= 0.049)

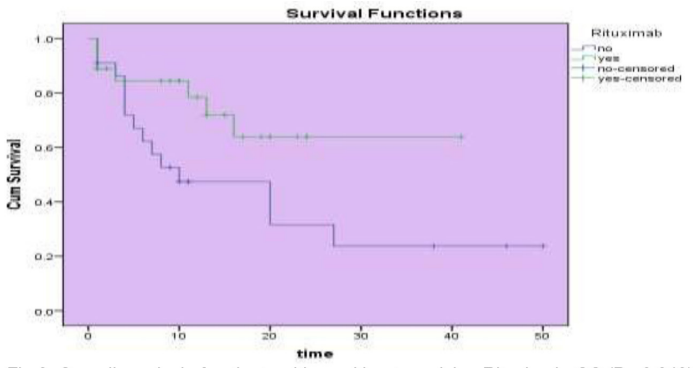
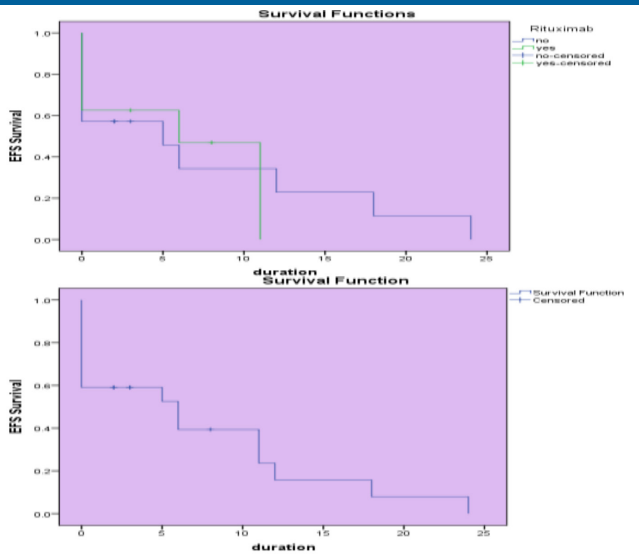


Fig. 4, Event free survival, there is no significant difference in duration to relapse or death between two groups of patients those who received rituximab and who did not, 4 patients were excluded as they deceased before they get treated.

Fig 4: Event free survival of patients with or without receiving rituximab, EFS (P= 0.2)



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According to table 2, there is no significant association regarding event free survival according to the gender, age, antigen expressions (CD10, CD7, CD7, CD13 and CD33), philadelphia chromosome positivity and inital WBC count in patients regardless to Rituximab intake.

Table 2: Event free survival of patients with or without receiving Rituximab (Cox regression).

Variables	HR	CI 95%		P
Gender	1.025	0.657 -	11.825	0.165
CALLA (CD10)	0.490	0.054 -	6.915	0.692
Aberrent antigen Expression (CD7,CD13,CD33)	0.593	0.084 -	3.616	0.536
Ph+ve B-ALL	0.472	0.120 -	3.230	0.574
Age (years)	0.434	0.134 -	3.128	0.589
WBC	0.632	0.159 -	1.774	0.304

P-value ≤ 0.05 (significant).

CALLA: Common acute lymphoblastic leukemia antigen. Ph: philadelphia chromosome. WBC> 30×10^9/L.

According to table 3, there is no significant association regarding overall survival according to the age, antigen expressions (CD10, CD7, CD7, CD13 and CD33), philadelphia chromosome positivity and inital WBC count in patients regardless to Rituximab intake, whereas there is significant association in overall survival according to the patient's age regardless of Rituximab intake (P=0.049).

Table 3: Overall survival of patients with or without take Rituximab (Cox regression).

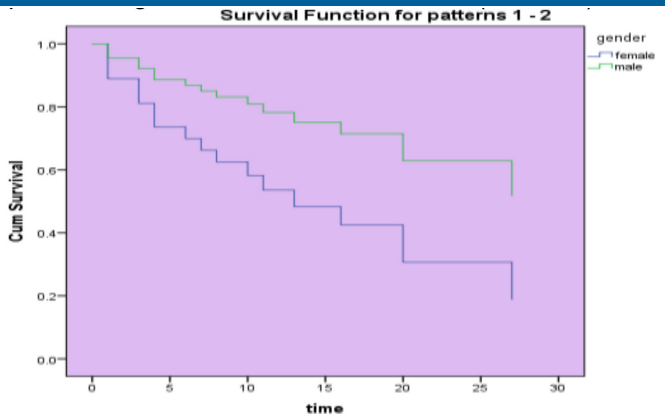
Variables	HR	CI 95%	P
Gender	0.933	0.974 - 6.630	0.049
CALLA (CD10)	0.343	0.092 - 5.495	0.74
Aberrent antigen Expression (CD7,CD13,CD33)	0.964	0.342 - 20.134	0.35
Ph+ve B-ALL	0.283	0.169 - 10.401	0.78
Age (years)	0.23	0.451 - 3.574	0.65
WBC	0.83	0.785 - 6.738	0.12

P-value ≤ 0.05 (significant).

CALLA: Common acute lymphoblastic leukemia antigen. Ph: philadelphia chromosome. WBC> 30×109/L.

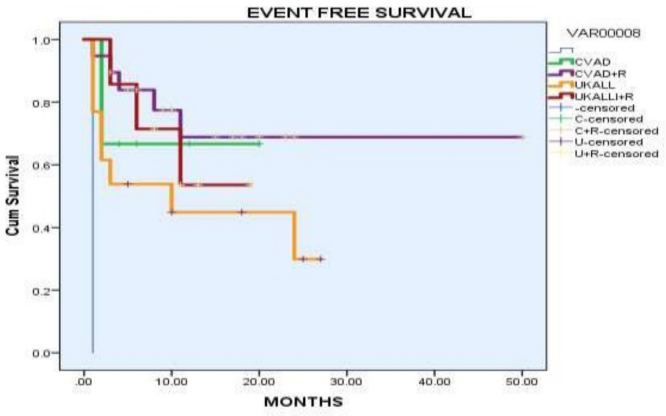
According to fig 5 there is significant difference in overall survival and male gender in patients regardless to Rituximab intake (P=0.049).

Fig 5: Difference in overall survival according to the gender.



According to fig 6 there is significant association regarding Event free survival in patients who received R-hyperCVAD (=36 months) comparing with other regimens such as R-UKALL (=13 months).

Fig 6: Event free survival between patients received different regimens with or without rituximab.



According to table (4); there is significant association between survival per year and Rituximab taken, (50%) of the patients who received rituximab were survive in the first year, (45%,5%) in the second and third years respectively. Whereas (57.1%) of the patients who did not receive rituximab survive in the first year, (0%) in the second year, (42.8%) survived in the third year as they maintained remission by allogenic bone marrow transplantation.

Table 4: Association between survival per year and Rituximab taken.

variables		Rituximab		P-value
		without	with	
	first year	4	10	
	%	57.1%	50.0%	
	2nd year	0	9	
Year	%	0.0%	45.0%	0.018
	3rd year	3	1	
	%	42.8%	5.0%	
	Total	7	20	
	%	100.0%	100.0%	

P-value ≤0.05 (significant).

Discussion

This single center analytic cross-sectional study conducted at the Baghdad Hematology Teaching Center in Iraq focused on precursor B-lineage acute lymphoblastic leukemia (B-ALL). The study used flow cytometric immunophenotyping (FCI) for diagnosis and patient follow-up. This method revealed CD20 expression in the patient cohort and detected BCR/ABL1 gene rearrangements in 10.2% of the participants[20,21]. The study examined the impact of CD20 expression and the incorporation of targeted therapy agents like Rituximab into chemotherapy regimens for disease management[8]. It revealed that 55% of the participants were treated with Rituximab. The study also found that the mean age of patients was 33, and the male to female ratio was approximately 1.8:1[22,23]. In general, CD20 expression is observed in 30-50% of BCP-ALL cases[24,25]. In this study, additional antigens affecting the prognosis of B-ALL, such as CD10 expression and aberrant expressions (CD33, CD13, CD7), were also detected in 89.8% and 14.3% of the patients, respectively[26,27]. The research in mutation and diseases problem in gens have been done in[28,29], they reviewed possible mutations in the populations. Results revealed that the addition of Rituximab improved the overall survival rate. Participants who were treated with Rituximab and chemotherapy had a mean survival of 35 months, which was significantly better than those who received chemotherapy alone (11 months, p=.005)[30,31]. Despite the potential benefits of Rituximab treatment, the impact of other factors, like age, high white blood cell count, and Philadelphia positive patents, on survival rates were inconclusive, possibly due to the study's small sample size and lack of initial cytogenetic stratification[32]. Nonetheless, the study found that participants who received Rituximab combined with the hyper-CVAD or UKALL protocol showed significantly longer event-free survival[33,34]. The study acknowledges limitations such as small sample size and the lack of consideration for other prognostic parameters, including cytogenetics apart from the Philadelphia chromosome[33]. Therefore, it recommends larger, prospective studies for better specification of disease-free and overall survival.

Conclusions

Based on study results, we concluded the following: Patients who received rituximab had better overall survival. No effect for age, WBC, antigen aberrant expressions on overall survival, while there is significant association with the male gender. No significant difference in event free survival between patients who received rituximab and patients who did not. There is significant association between survival per year and Rituximab therapy.

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