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Assessment of the short term outcomes of different chemotherapy protocols in adult acute lymphoblastic leukemia patients at Baghdad Teaching Hospital

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General Note

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is a neoplastic disease of immature lymphocytes or lymphocyte progenitor cells for either the B or T cell lineage, multiple induction ways have been developed for adult patients with acute lymphoblastic leukemia (ALL). Though, only a few prospective randomized trials have directly paralleled these regimens with their outcome results. *Aims of the study:* Assessment of the response rate of adult patients treated with UKALL protocols and Hyper-CVAD protocol in acute lymphoblastic leukemia patients, and the impact of different prognostic factors on outcome. *Patients and methods:* A prospective cohort study conducted in the hematology unit of Baghdad Teaching Hospital on 47 adult ALL patients treated with either UKALL (United Kingdom Acute Lymphoblastic Leukemia include UKAL12, UKALL11"B, C") or hyper-CVAD (hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) protocols between March 2016 and May 2017 with mean follow-up of 6.16 months. *Results:* This study included 47 adult patients with the mean age of (23.9 years) with the male: female ratio of (2.1:1). Complete remission after induction therapy was achieved in 66.7% and 79.3% of the patients by hyper-CVAD and UKALL, respectively. The mortality rate was 16.0% and 6.89% for hyper-CVAD and UKALL respectively, while the eight months OS and PFS was 84% and 65% for hyper-CVAD and 78% and 62% for UKALLs. *Conclusion:* Although our study was short duration with small sample size, it was able to show the efficacy of both hyper-CVAD and UKALLs protocols in the treatment of Philadelphia negative ALL, with good initial complete remission mainly after induction phase. There was no difference in the response rate between both studied protocols according to different age groups (above or below 25 years old).

Keywords: Hematology, Chemotherapy, ALL, Hyper-CVAD, UKALLs,

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a neoplastic disease of the immature lymphocytes (Faderl et al., 2010), which remains the challenging malignancies of the adult in relations to the treatment (Al-Khabori et al., 2010). Different induction regimens developed for adult patients with ALL, but only little prospective trials have been directly compared these regimens (Chang et al., 2008). The incidence of ALL in the united states was 1.6 over 100,000 (Jemal et al., 2017) while ALL was the fifth most common malignancy affecting the Iraqi population, where the incidence was 5.95 % of all record malignant cases according to the Iraqi Cancer Registry 2009 (Health, 2009). In general, the treatment strategies for ALL consist of induction remission, consolidation, and maintenance phase, when the induction had the highest risk time during treatment, and they should be monitored closely with death rates range from 2–20%, depending on the specific protocol used and the patient's age. Most induction deaths because of either severe bacterial sepsis and also fungal infection (AV, 2016 Jan 19).

The progress in chemotherapy regimens with the United Kingdom Acute Lymphoblastic Leukemia (UKALL) trials and the brief regimen with hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone (Hyper-CVAD)/HD MTX - c (high-dose methotrexate plus cytarabine) which shown promising result concerning the complete remission (Rowe et al., 2005; Bassan and Hoelzer, 2011). The landscape of treatment was further changed by the developing of post-remission programs, targeting therapy, monoclonal antibodies (Thomas et al., 2010; Topp et al., 2011), and the MDR technique (Bassan et al., 2009). Several genetic and clinical impact identified as poor prognostic factors in ALL (Hoelzer et al., 1988) including advancing age (>35 or >60), higher white cell count and the presence of CNS disease at diagnosis time, specific cytogenetic abnormalities, certain immunophenotypes and the time to achieve complete remission are significant prognostic to the outcome in ALL (Le et al., 2006), which detect the early clearance from leukemic blast, which have a excellent heuristic power, therefore, initial CR within 4 weeks of starting regimen or after one course of induction chemotherapy should be achieved mainly for patients with standard or high-risk disease and failure to reach to the CR has been considered an independent unfavorable prognostic factor, confirmed in most adult ALL studies (Larson et al., 1995).

2. PATIENTS & METHODS

This is a prospective cohort study, and it was conducted at Haematology unit of Baghdad Teaching Hospital–Medical City, from March 2016 to May 2017 with medium follow up 6.16 months, where 47 patients with Philadelphia negative ALL, received different ALL protocol therapy according to local protocol guideline of the unit.

Methods

The patients referred and admitted to the hematology unit of Baghdad teaching hospital, in which the diagnosis made by consultant hematologists according to baseline protocol of the hematology unit, which depends on morphology and immunophenotype of the PB and/or BMA. The BCR-ABL fusion gene is excluded by using FISH analysis to rule out Philadelphia positive ALL.

Data obtained for each patient from their records by using the form of a database. All patients with ALL were treated with either hyper-CVAD protocol (n=18) or UKALLs protocols (UKALL12, UKALL11 (B, C)) (n=29), according to the decision of the hematologist responsible for treating each case as shown in figure 1.

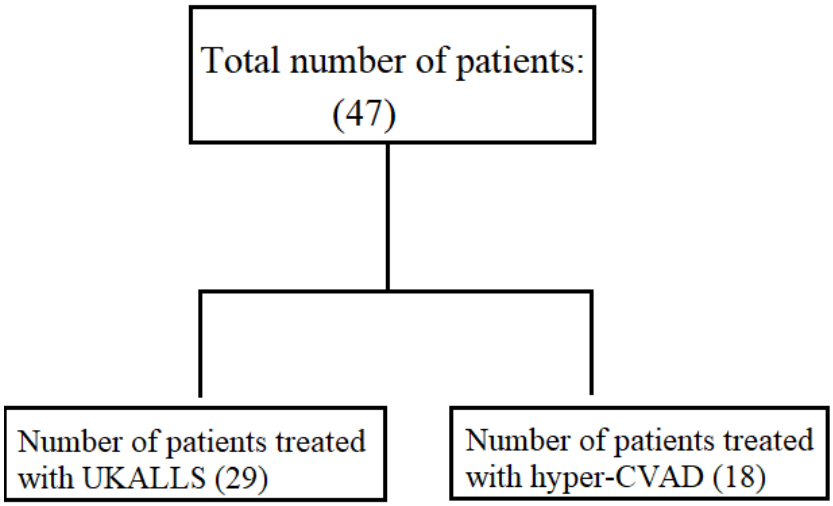

Figure 1 Scheme diagram describes the number of patients and protocol distribution

The assessments

1. All ALL patients were assessed for response achievement after induction phase according the protocol recommendation (hyper CVAD after 2 cycles while in UKALLs after two phases of induction), the assessment made by bone marrow aspiration study after the peripheral blood indices recovery (hemoglobin ≧ 10g/dl, ANC ⩾ 1500mml, and platelets count ≧ 100x109 with disappearance of blast from peripheral blood). Accordingly, the response type was categorized according to the number of blasts in bone marrow after completion of induction phase for each protocol as follows:
    a. Complete remission: is the presence of less than 5% of blasts in bone marrow aspiration (BMA) study.
    b. Partial response is the presence of 5-25% of a blast in BMA.
    c. No response if the presence of more than 25% of a blast in BMA.
    d. Death documented at any time of the study period.
2. In general, if any patient had more than 5% of blasts after induction treatment or at any time of the study, it was considered as refractory ALL.
3. The toxicity of chemotherapy of each protocol was assessed (according to Common Terminology Criteria for Adverse Events (CTCAE)) during the induction phase.
4. All patients followed to the last date of the study to assess the overall survival (as defined from time study entry to death or date of the last follow-up). Disease-free survival (DFS) defined as the survival from the CR till date of relapse, last date of observation or death.

3. RESULTS

Patient's characteristics

There were 47 adults patients with de novo ALL - Philadelphia chromosome-negative, of these patients sample, (32) patients were male and (15) patients were female, with a male to female ratio 2.1:1, while the meantime of follow up was 6.16 (2.6-13.9) months, the patients characteristic are summarized in table 1.

Table 1 Characteristics summary of all ALL patients (n=47)

Variables		Hyper CVAD (n=18)	UKALLs (n=29)
Age	<25 years	8(44.4%)	23(79.3%)
	≥25 years	10(55.5%)	6(20.6%)
Gender	Female	5(27.7%)	10(34.4%)
	Male	13(72.2%)	19(65.5%)
Type of ALL	B type	10(55.5%)	17(58.6%)
	T type	8(44.4%)	12(41.3%)
Baseline WBC	Low risk	13(72.2%)	19(65.5%)
	High risk	5(27.7%)	10(34.4%)

*low risk (B-ALL WBC less than 30×10^9/L, T-ALL WBC less than 100×10^9/L), high risk (B-ALL WBC more than 30×10^9 /L and T-ALL more than 100×10^9/L) (7).

The response rate

1. The response rate in relation to different predictors after induction phase.

Thirty-five out of 47 patients (74.5%) were achieved the first complete remission (CR) while there were 12 patients (25.5%) not achieved the remission, as shown in table 2.

Table 2 Remission status of ALL patients after induction phase

Remission status	Value no.(%)
Complete remission	35 (74.5%)
Incomplete remission	12 (25.5%)

2. The response rate in relation to different predictors parameters after the end phase of induction for all patients with different settings.

This analysis focused on important prognostic factors which may influence the outcome of response in ALL, after the induction phase. These parameters are age, gender, type of ALL, WBC count and the type of protocol used, as illustrate in Table 3.

Table 3 Assessment of predictors of complete response after the induction

Variable		CR	Not CR	RR (95%CI)	P value
Age	<25 years	23 (74.2%)	8 (25.8%)	1.032 (0.396-2.92)	1.0
	≥25 years	12 (75.0%)	4 (25.0%)		

Gender	Female	10 (66.7%)	5 (33.3%)	1.524 (0.573-3.803)	0.481
	Male	25 (78.1%)	7 (21.9%)		
Type of ALL	B type	17 (63.0%)	10 (37.0%)	3.704 (1.077-14.200)	0.047
	T type	18 (90.0%)	2 (10.0%)		
Baseline WBC	Low risk	24 (75.0%)	8 (25.0%)	0.938 (0.363-2.653)	1.0
	High risk	11 (73.3%)	4 (26.7%)		
Type of protocol	HyperCVAD	12 (66.7%)	6 (33.3%)	1.611 (0.621-4.092)	0.493
	UKALL	23 (79.3%)	6 (20.7%)		
RR: relative risk, CI: confidence interval					

The response rate in relation to different predictors' parameters for all patients with different parameters at the end of the study

The effect of prognostic factors on the type of response at the end of the study was illustrated in table 4.

Table 4 Assessment of predictors of sustained remission at the end of the study

Variables		Still in CR	Not CR	RR (95%CI)	P-value
Age	<25 years	20 (64.5%)	11 (35.5%)	1.032 (0.671-1.753)	1.0
	≥25 years	10 (62.5%)	6 (37.5%)		
Gender	Female	8 (53.3%)	7 (46.7%)	0.776 (0.423-1.231)	0.344
	Male	22 (68.8%)	10 (31.3%)		
Type of ALL	B type	16 (59.3%)	11 (40.7%)	0.8447 (0.542-1.333)	0.546
	T type	14 (70.0%)	6 (30.0%)		
Baseline WBC	Low risk	21 (65.6%)	11 (34.4%)	1.094 (0.706-1.917)	0.753
	High risk	9 (60.0%)	6 (40.0%)		
Type of protocol	UKALL	20 (69.0%)	8 (44.4%)	0.806 (0.469-1.256)	0.371
	hyperCVAD	10 (55.6%)	9 (31.0%)		
RR: relative risk, CI: confidence interval					

Assessment type of protocol treatment according to the response rate after induction therapy in correlation to other prognostic parameters

The table 5 demonstrate the outcome of different type of protocols (UKALLs and hyper-CVAD) used for treatment of ALL patients in relation to diverse age group (> or ≤ 25years)(adult ALL versus AYALL), gender (male vs. female), type of ALL (T-lineage ALL vs. B-lineage ALL) and WBCs count (high risk vs. low risk).

Table 5 Association between various predictors and response rate with different types of protocol treatment

Protocols type	Variables	CR	Not CR	P-value
hyperCVAD	<25 years	6 (75.0%)	2 (25.0%)	0.638
	≥25 years	6 (60.0%)	4 (40.0%)	
UKALL	<25 years	17 (73.9%)	6 (26.1%)	0.295
	≥25 years	6 (100.0%)	0 (0.0%)	
hyper-CVAD	Female	1 (20.0%)	4 (80.0%)	0.022
	Male	11 (84.6%)	2 (15.4%)	
UKALL	Female	9 (90.0%)	1 (10.0%)	0.633
	Male	14 (73.7%)	5 (26.3%)	
HyperCVAD	B type	5 (50.0%)	5 (50.0%)	0.152
	T type	7 (87.5%)	1 (12.5%)	
UKALL	B type	12 (70.6%)	5 (29.4%)	0.354
	T type	11 (91.7%)	1 (8.3%)	
hyperCVAD	Low risk WBC	9 (69.2%)	4 (30.8%)	1.0
	High risk WBC	3 (60.0%)	2 (40.0%)	
UKALL	Low risk WBC	15 (78.9%)	4 (21.1%)	1.0
	High risk WBC	8 (80.0%)	2 (20.0%)	

Overall survival assessment by multivariate analysis in relation to the different patients' parameters

The cumulative meantime of OS was (10.0±0.811) months for all ALL patients. Table 6 illustrating the hazard ratio of each predictor factor after excluding the effect of the other variable in the module, those factors are the age, gender, baseline WBCs count, type of the ALL, type of the induction chemotherapy protocol, remission status and period between diagnosis of ALL and starting treatment, as demonstrating in figures (2,3,4,5,6) respectively.

Table 6 Final model for predicting OS (multivariate cox proportional)

Variables	HR	95% CI for HR	P value
Age (≤ vs. > 25 years)	0.758	0.189 - 3.032	0.695
Gender (female vs. male)	1.369	0.379 - 4.943	0.632
Baseline WBC (low vs. high risk)	0.618	0.183 - 2.089	0.439
Duration before initiation induction (days)	0.959	0.836 - 1.100	0.551
Remission status (not CR vs. CR)	40.592	7.995 - 206.104	0.001

Type of ALL (B.ALL vs. T.ALL)	1.507	0.440 - 5.163	0.513
Type of induction chemotherapy (hyper-CVAD vs. UKALLs)	0.721	0.166 - 3.126	0.662
Multivariate Cox proportional analysis was performed			

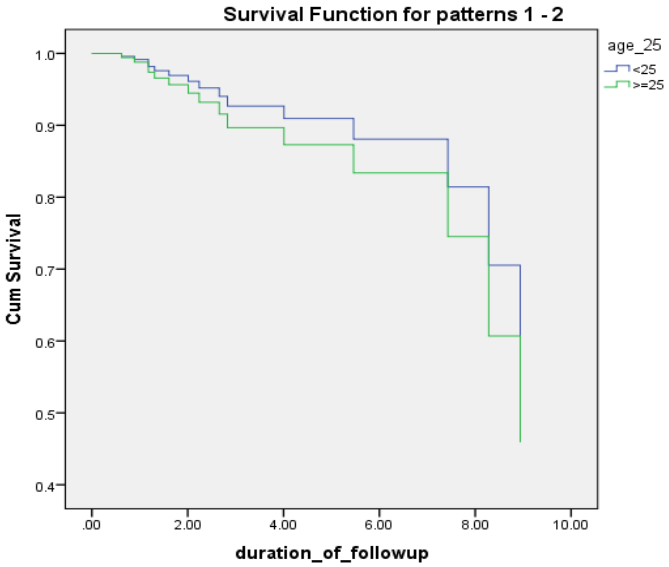

Figure 2 Overall survival of ALL patients according to age (p-value=0.613)

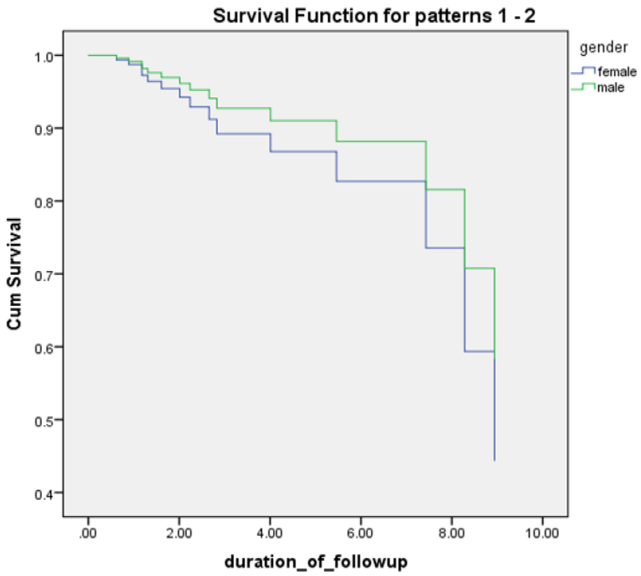

Figure 3 Overall survival of ALL patients according to gender (p-value=0.554)

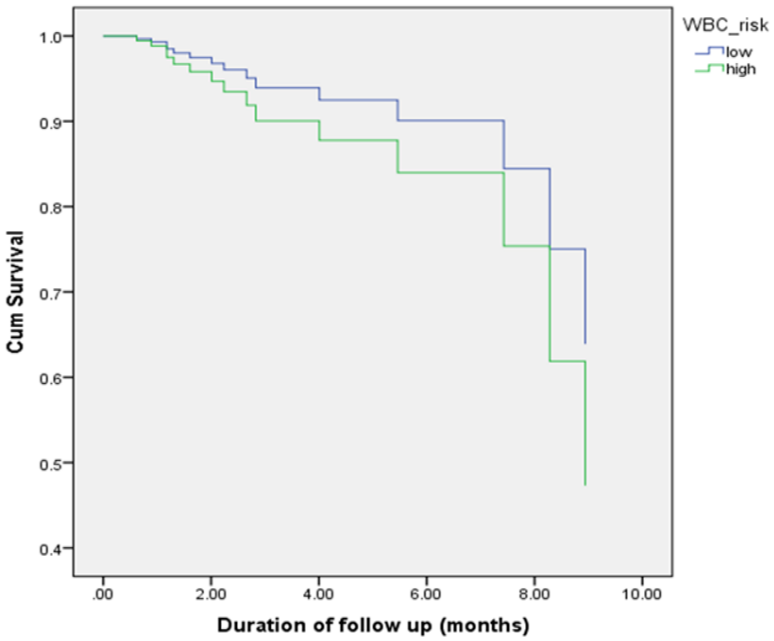

Figure 4 Overall survival of ALL patients according to WBC count (p-value=0.439)

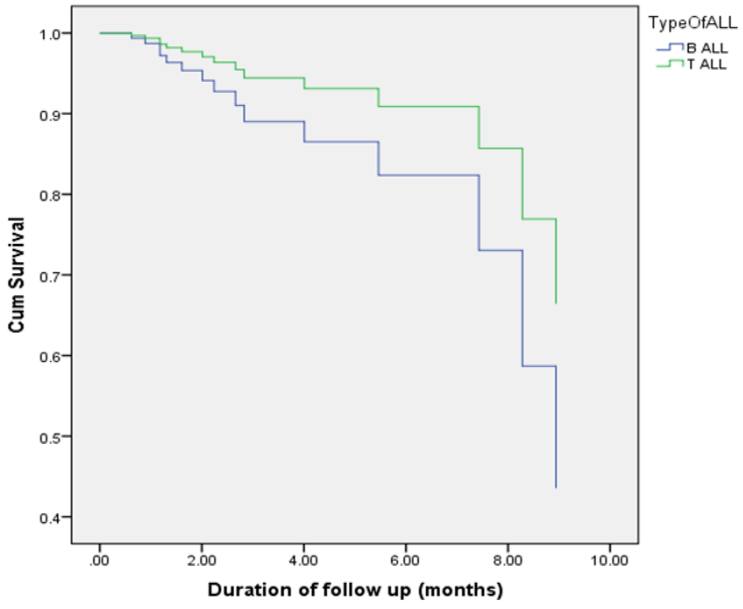

Figure 5 Overall survival of ALL patients according to the cell type of ALL (p-value=0.387)

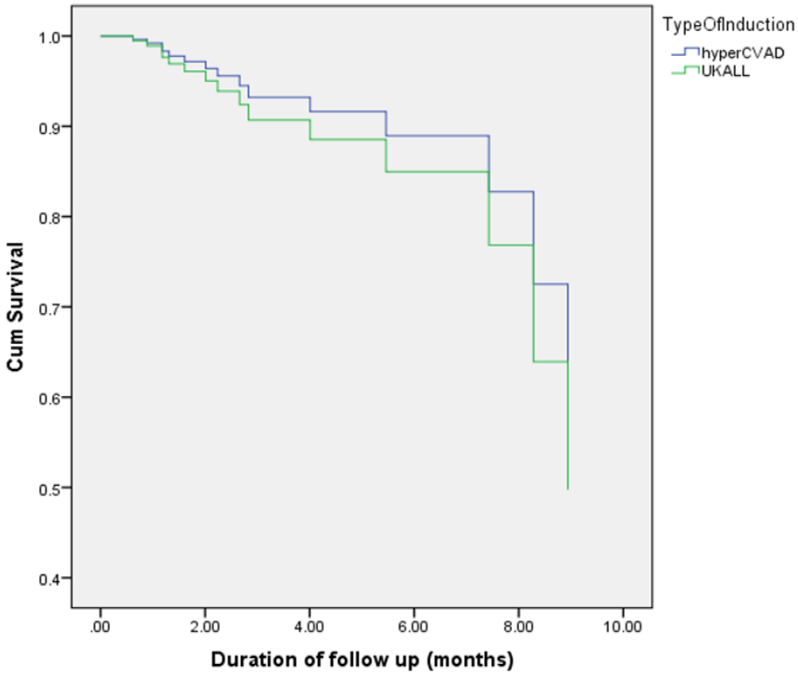

Figure 6 Overall survival of ALL patients according to the type of protocol (p-value=0.660)

Progression-free survival (PFS) analysis

The cumulative meantime for progression-free survival (PFS) present was (9.587 ± 0.818) months (95%CI, 7.984-11.189), the table 7 which show the effect of different predictor factors on the PFS with the hazards ratio. (Fig. 7 Showed the Progressive free survival of ALL patients according to protocol type of chemotherapy).

Table 7 The cumulative meantime for progression-free survival for ALL patients

Predictors	Mean ± SEM	HR	P-value
PFS	9.587 ± 0.818		
Type of ALL			
B – ALL	8.723 ± 1.164	1.881	0.216
T – ALL	10.806 ± 1.015		
Type of induction chemotherapy			
Hyper-CVAD	9.174 ± 1.270	1.240	0.661
UKALL	9.510 ± 0.988		
Gender			
Female	5.936 ± 0.943	1.938	0.185
Male	10.307 ± 0.928		
Age			
<25 years	9.532 ± 1.009	1.027	0.958

≥25 years	9.613 ± 1.365		
Remission status			
Complete response	12.238 ± 0.662	0.037	<0.001
Partial response	5.030 ± 2.400	0.531	0.471
No response	2.924 ± 0.816	1.0	-
Baseline WBC			
Low-risk WBC	9.885 ± 0.957	0.750	0.573
High-risk WBC	7.527 ± 1.152		
Kaplan Meir analysis was performed			

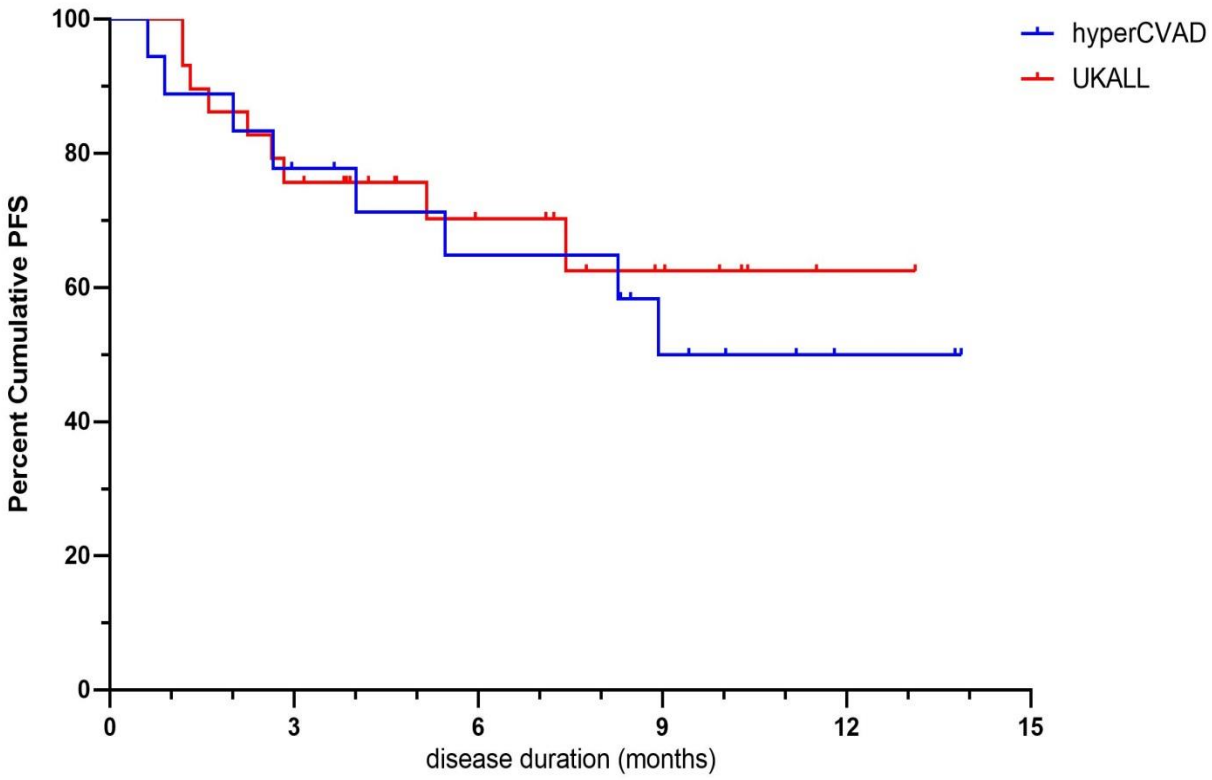

Figure 7 progressive free survivals of ALL patients according to the protocol type of chemotherapy

Mortality rate

1. Assessment of the mortality rate post-induction treatment

The mortality rate post-induction treatment in association with other prognostics parameters is shown in table (8).

Table 8 Assessment of the mortality rate with prognostic parameters post-induction treatment

	Survived	Death	P-value	(95%CI)
Treatment				
HyperCVAD	15 (83.3%)	3 (16.0%)	0.356	(0.647-1.110)
UKALL	27 (93.1%)	2 (6.89%)		
Type of ALL				
B-ALL	22 (81.4%)	5 (18.5%)	0.063	(0.633-0.987)
T-ALL	20 (100%)	0 (0.0%)		
Age				
<25	28 (90.3%)	3 (9.6%)	1.0	(0.833-1.428)
≥25	14 (87.5%)	2 (12.5%)		
Gender				
Female	14 (93.3%)	1 (6.6%)	1.0	(0.791-1.318)
Male	28 (87.5%)	4 (12.5%)		
CI: confidence interval				

2. Assessment of the mortality rate of ALL patients at the end of the study

The mortality rate at the end of the study in association with the different prognostics parameters of ALL patients is shown in table 9).

Table 9 Assessment of predictors of mortality rate at the end of the study

	Survived	Death	P-value	(95%CI)
Treatment				
Hyper-CVAD	15 (83.0%)	3 (16.0%)	1.0	(0.717-1.324)
UKALL	24 (82.7%)	5 (17.2%)		
Type of ALL				
B-ALL	21 (77.7%)	6 (22.3%)	0.437	(0.723-1.206)
T-ALL	18 (90.0%)	2 (20.0%)		
Age				
<25	26 (83.8%)	5 (16.1%)	0.821	(0.789-1.501)
≥25	13 (81.2%)	3 (18.7%)		
Gender				
Female	12 (80.0%)	3 (20.0%)	0.710	(0.638-1.240)

Male	27 (84.3%)	5 (15.6%)		
CI: confidence interval				

Toxicity of chemotherapy

The toxicity of chemotherapy of each protocol assessed according to common terminology criteria for adverse events, as shown in table 10.

Table 10 The toxicity of chemotherapy during the induction phase of each of UKALLs and Hyper-CVAD. (Grade 1-5)

	hyper-CVAD	UKALL	P-value
Number	18	29	-
Mucocutaneous	9 (50.0%)	16 (55.2%)	0.730
Diarrhea	5 (27.8%)	3 (10.3%)	0.230
Constipation	4 (22.2%)	12 (41.4%)	0.178
Anal pain	6 (33.3%)	4 (13.8%)	0.112
Nausea	16 (88.9%)	21 (72.4%)	0.180
Vomiting	12 (66.7%)	16 (55.2%)	0.435
febrile neutropenia	17 (94.4%)	18 (62.1%)	0.013
Pruritus	4 (22.2%)	2 (6.9%)	0.185
Headache	9 (50.0%)	16 (55.2%)	0.730
Alopecia	15 (83.3%)	24 (85.7%)	1.0
Hyperglycemia	2 (11.1%)	6 (21.4%)	0.453
WBC decreased	15 (83.3%)	25 (86.2%)	1.0
Low platelet	16 (88.9%)	23 (79.3%)	0.692
Anemia	15 (83.3%)	24 (82.8%)	1.0
Bruising	2 (11.1%)	6 (21.4%)	0.453
Appendicitis	0 (0.0%)	1 (3.4%)	1.0
Neuropathy	0 (0.0%)	11 (39.3%)	0.002

4. DISCUSSION

In this prospective cohort study, 47 patients with de novo Philadelphia chromosome-negative ALL, 29 (61.7%) of them were treated with one of UKALLs protocol while the other 18 (38.3%) patients treated with hyper-CVAD protocol, with a mean follow-up of 6.16 (2.6-13.9) months. Mean age of the studied population was (23.9±10.7) years which appear that majority of patients are young below 25 years old, and this is similar to other studies Ali M. Jawad et al., Karantijian et al., Shaikh et al. and Farsi (Ali M Jawad, 2003, Kantarjian et al., 2004, Shaikh et al., 2011, Farsi, 2017). The male gender seems to be more predominance than female gender with male to female ratio 2.1:1 which is agreed to the many other studies (E, 2012., Kantarjian et al., 2004, Deffis-Court et al., 2013) also.

The B-cell lineage ALL was found in (57.4%), which is higher than T-cell lineage ALL (42.6%), while in Shaikh et al. and Sive et al. studies (Sive et al., 2012, Shaikh et al., 2011), the percentage of T-cell ALL were 17.4% and 19%, subsequently. This difference may be due to geographical variation of ALL subtypes and may be due to small number of our patients' sample too.

In this study, the mean WBC count of our research was 22.9x109, most of our patients (68.1%) were with low risk WBC count, this is comparable to other studies (Shaikh et al., 2011, Magrath et al., 2005). The first assessment response to Hyper-CVAD and UKALLs chemotherapy protocol was done at the end of induction treatment of each protocol and showed complete remission in 74.5% of all patients. Of those patients, 66.7% and 79.3% had CR by Hyper-CVAD and UKALLs subsequently, without significance difference (p-value= 0.493). Male ALL patients who received hyper-CVAD protocol was significant CR than females gender (p-value 0.022), while there was no significantly different effect among both genders who received UKALL protocol treatment. Also, there was no significant predominance benefit of both protocols among all different age groups, type of cell lineage and initial WBC count of ALL patients.

Regardless type of chemotherapy protocols used, the post-induction response assessment shows that there was higher significance CR in T-cell lineage ALL over B-cell lineage ALL with p-value (0.047), this is similar to what found in other studies (Gökbuget N, 2001, JM, 2011) while in Shaikh et al. review (Shaikh et al., 2011) the preferable effect was in B-cell ALL type, this result may be related to the different distribution of maturation stage of T- cell lineage. The CR response at the end of the study for each hyper-CVAD and UKALLs protocols was 55.6%, 69.0% respectively, again without significant difference among all age groups, genders, type of cells and initial WBCs count. Accordingly, the choice of protocols according the studied prognostic parameters (age groups, genders, type of cells and initial WBCs counts) may have no benefits regarding the response rate.

In the current study, the cumulative meantime of OS was (10.0±0.811) months for all ALL patients. The primary multivariate analysis of overall survival showed eight months OS was 84%, 78% for both hyper-CVAD and UKALLs proto-cols respectively, with HR 0.721, as there is higher outcome for hyper-CVAD than UKALLs protocol although there was no significant difference (p-value 0.662).

The younger patients (≤ 25 years old) and those ALL patients with low WBC count (low risk group) had better outcome with HR 0.7, 0.6 fold respectively, than older patients and those with high WBC counts, although it didn't show statistical significance as shown in Karantijian et al., Shaikh et al. (Kantarjian et al., 2004, Shaikh et al., 2011). While the female gender patients showed a modest effect on OS as there was slightly lower survival by 1.369 fold than male patients, in contrast to other studies (Kantarjian et al., 2004, Shaikh et al., 2011) with non-significant p-value, this may be related to another risk factor such as degree of cytogenetic abnormalities which is not evaluated in this study. The only highly significant survival was found among patients in relation with remission status, as patients who didn't achieve the CR was found to be less survival with 40.592 folds than those achieved CR which was highly significant with p-value 0.001.

Our study showed there was some improvement in OS among ALL patients with short time period between the diagnosis and time of initiating induction therapy with HR 0.959, although it was not statistically significant, as the longer period may be associated with increased degree of BM failure and more therapy complications while that patient with T-cell ALL had better overall survival than B-cell lineage ALL patients (HR=1.5, p-value 0.5).

The cumulative meantime for progression-free survival(PFS) for all patients was (9.587 ± 0.818) months and the eight months PFS was 65%, 62% for both hyper-CVAD and UKALLs protocols with 1.240-fold higher rate of PFS among patients received UKALLs protocol versus hyper-CVAD protocol, but without statistical significance. The duration of PFS was found to be slightly higher among T cell ALL patients (10.806 ± 1.015) months compare to B-cell ALL patients (8.723 ± 1.164) months with HR of 1.881 and p-value = 0.216. Again there was no significant statistical difference in PFS for those of different genders and age groups.

In our study there were 5 patients (10.6%) died before the first assessment and the mortality rate was slightly higher in hyper-CVAD protocol (16.0%) which was less than the mortality rate in Mexican study (22.2%) (Ramos-Penafiel et al., 2014) and higher than the mortality rate in Chinese study (13.2%) (Xu et al., 2008). While there was only 6.8% death among patients used UKALLs protocol, this result was close to the result of Shaikh et al. (7.4%) (Shaikh et al., 2011). This difference although it was not significant but more intensive and high dose therapeutic regimen may be relating to this mortality rate in hyper-CVAD protocol besides the availability of supportive care during treatment induction. At the end of study we found that the mortality rate increase in UKALLs to (17.2%) and still the same in hyper-CVAD (16.0%) without significant difference and this is maybe relating to using higher dose of chemotherapy and addition new drugs to protocol post-induction treatment in UKALLs protocol. There was no significant difference observed in the mortality rate among all different studied prognosis parameters at the end of the study.

According to common terminology criteria for adverse events, the side effect of chemotherapy expected with severe; prolonged myelo suppression was universal. Common toxicities included febrile neutropenia which showed significant worst in patients on

hyper-CVAD than UKALLs protocols that may be due to more dose-intensive chemotherapy while the neuropathy shows significant worst effect in UKALLs protocol than hyper-CVAD protocol, which may be related to more using vincristine therapy during induction phase of UKALLs protocol. Other side effects including mucositis, diarrhea, constipation, anal pain, GIT upset, pruritus, headache, alopecia, hyperglycemia, WBC decreased low platelet, anemia, bruising, and appendicitis showed no significant difference between both protocols.

5. CONCLUSION AND RECOMMENDATIONS

Although the short duration with a small sample size of our study, it was able to show efficacy of both hyper-CVAD and UKALLs protocols in treatment of Philadelphia negative ALL, with good initial complete remission mainly after induction phase. There was no difference in the response rate between both studied protocols among different age groups, so we can say: the choice of chemotherapy protocol in treatment of ALL should be based on the haematologist experience and protocol familiarity with availability of drugs and presence of good supportive care, as the safety of both protocols were acceptable also. The higher response rate of T-cell lineage ALL after induction treatment may directing to look to B-cell type of ALL and the rule of addition of monoclonal therapy to increase the response rate. Again, the non-significant difference in response rate and OS between different prognostics parameters groups may give an idea to include other prognostic parameters like; cytogenetic, molecular analysis and early MRD negativity after induction therapy, in deciding which protocol is preferable with better outcome next time.

Therefore, further studies with longer time follow up and assess the MRD status after induction phase in relation to cytogenetic and molecular analysis are recommended to establish the optimal induction regimen for ALL adult patients, their benefit on OS and PFS and the cost-effectiveness of each protocol.

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Ethical Approval

Iraqi Board for Medical Specialization ethical approval committee letter at 8/28/2018, no.: 1105.

List of abbreviation

Abbreviation	Wards
ALL	Acute Lymphoblastic Leukemia
AYA	Adult and young adult
BM	Bone marrow
CBC	Complete blood count
CD	Cluster of differenatition
CNS	Central nervous system
CR	Complete Remission
DFS	Disease Free Survival
ECOG	Eastern Cooperative Oncology Group
EGIL	European Group for the Immunological classification of Leukemias
FAB	French–American–British
HSCT	Haematopoietic stem cell transplantation
Hyper-CVAD	Hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
MPO	Myeloperoxidase
MRC	Medical research council
MRD	Minimal residual disease

NCCN	National Comprehensive Cancer Network
NHS	National Health Service
OS	Overall Survival
PAS	Periodic acid Schiff stain
PCR	Polymerase chain reaction analysis
Ph	Philadelphia chromosome positive
RFS	Relapse free survival
SmIg	Surface membrane immunoglobulin
TCR	T-cell receptor
TdT	Terminal deoxynucleotidyl transferase
TKI	Tyrosine kinase inhibitor
UKALL	United Kingdom Acute Lymphoblastic Leukemia
WBC	White blood cell count
WHO	World Health Organization

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