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ORIGINAL ARTICLE

The outcome of B-cell Non-Hodgkin's lymphoma in Patients treated with modified UKCCSG FAB LMB 96 protocol: A single center experience

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ABSTRACT

Background: Non-Hodgkin lymphoma (NHL) results from the malignant proliferation of cells of lymphocytic lineage.

Objectives: To assess the outcome of B-cell non-Hodgkin 's lymphoma in children treated with modified FAB LMB 96 protocol.

Methods: This descriptive retrospective study for 103 patients <14 years with B-cell non-Hodgkin's lymphoma in Child Central Teaching Hospital from 1st January 2010 to 31 December 2014. All cases were treated with the Modified FAB LMB 96 protocol. According to modified UKCCSG NHL FAB 96 PROTOCOL: patients was divided into low risk (group A) which includes (completely resected stage I tumor and completely resected abdominal stage II tumor); intermediate risk (group B) which include (unresected stage I &II , resected stage II other than abdominal completely resected tumor and stage III) ; and high risk (group C) which include (patients with BM involvement >5% , CNS involvement , or both).

Results: All patients were treated with modified FAB LMB 96 Protocol; group A (1%,) group B (89%) and group C (10%), final outcome in this study shows; sixty-five (63.1%) achieved continuous complete remission ,27 (26.2%) died, 11(10.67%) loss of follow up, most common causes of death were sepsis (51.8 %) and tumor lysis syndrome (22.2%) mainly during or post COP1 (29.6)% and COPADM1(25.9) %, event free survival and overall survival were (59.5)%and (68.4 %) respectively ,there is a significant relation between event free survival and histopathological subtypes, stages and risk group protocol of B-cell Non-Hodgkin 's lymphoma.

Conclusions: Pediatric patients with B-cell NHL who treated by modified UKCCSG FAB LMB 96 protocols display an improved event-free survival and overall survival. The outcome was significantly better in Burkitt's lymphoma and children with tumor stages (I, II, III), and risk group (A). Sepsis and Tumor lysis syndrome were the most common cause of death.

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Keywords Children, FAB LMB 96 protocols, Lymphoma, Non-Hodgkin, Outcome.

INTRODUCTION

Non-Hodgins's lymphoma (NHL) is the most common hematological malignancy worldwide, accounting for nearly 3% of cancer diagnoses and deaths [1 2] .It results from the malignant proliferation of cells of the lymphocytic lineage [3] . Although the exact incidence of NHL in the pediatric age group is unknown, previous studies showed an increase in the overall incidence of NHL which varies with the age of the child, increasing progressively from birth to the older age group[4 5] .

Cure rates of children with mature B-cell lymphoma, that is, mainly Burkitt, but also diffuse large B-cell lymphoma (DLBCL), have significantly improved over the past 25 years largely as documented by prospective studies, including the Lymphomes Malins B (LMB) studies of the French Society of Pediatric Oncology (SFOP)[6 7 8] . With current combination chemotherapy regimens, survival in pediatric age group is generally excellent (85 to over 90%) for all patients, including those with disseminated disease, bone marrow involvement, central nervous system (CNS) involvement, and those with high serum lactate dehydrogenase (LDH)[9 10] .

Children with NHL was previously managed according to the LMB 84 trial (1984-1987) [11] . In this protocol, the choice of treatment was depend mainly on stage as defined by Murphy at St Jude Children's Research Hospital that divide the patients involvement by the tumor into 4 stages with stage 1 involve tumors confined to single anatomical area, stage 2 is tumors that involve two anatomical area but on same side of the diaphragm and while tumors on opposite sides of diaphragms categorized as stage 3 .Patients of any stage if they had central nervous system (CNS) or bone morrow involvement classified as stage 4[12 13] . LDH level, although recognized for a long time as prognostic, but much correlated to stage, was not considered for treatment stratification, except in the German Berlin-Frankfurt-Münster (BFM) 90 and 95 strategies. In an attempt to achieve treatment reduction and improved survival, children were treated mainly by FAB/LMB96 (1996-2001) .

Children with NHL in Iraq are treated by the modified UKCCSG FAB LMB 96 protocol (United Kingdom Children Cancer Study Group Lymphomes Malins B 96) but the response rate to this protocol has not been studied, so this study aims to assess the outcome of B-cell NHL in children treated with modified UKCCSG FAB LMB 96 protocol and to identify the risk factors of B-cell NHL and their effect on the outcome.

METHODS

A retrospective descriptive study on 103 children <14 years of age newly diagnosed B-cell NHL who were admitted in haemato-oncology ward in Child's Central Teaching Hospital over 5 years between the 1st of January 2010 and 31 of December 2014. Patients were treated according to the modified UKCCSG NHL FAB LMB 96 protocols [6]. Supportive therapy was the mainstay of treatment before initiating chemotherapy and this included excessive hydration in 3000 cc / m^2 with allopurinol 100 mg / m^2 /day in three divided doses. This is continued till no risk of tumor lysis is apparent. Electrolytes with renal function monitoring were also followed during treatment to avoid the risk of tumor lysis syndrome. Other supportive care as blood products transfusion or antibiotics were given as indicated. Data were collected from patients records at the oncology ward and all patient assessment were done by senior pediatric oncologist.

According to the modified UKCCSG NHL FAB 96 Protocol: patients can be divided into low risk (group A) which include (completely resected stage I tumor and completely resected abdominal stage II tumor); intermediate risk (group B) which include (unresected stage I &II, resected stage II other than abdominal completely resected tumor and stage III); and high risk (group C) which include (patients with BM involvement >5%, CNS involvement, or both). This is modification according to the policy of the ward to get more benefit of chemotherapy for the patients with bone marrow involvement.

The details of the treatment of each group are seen in the Figures1,2,3&4. According to this protocol, patients receive a combination chemotherapy in cycles. Eight patients received two COP because of renal impairment and sepsis; one of them received CYM2 and loss of follow up, two patients achieved CCR, and five patients died. Unfortunately, the majority of patients were not subjected to tumor evaluation during treatment (after COP, before COPADM 2, before CYM2 of group B, after COP, before MiniCyve1 and before maintenance of group C).

The evaluation of patients is done after the end of his protocol, the patient is considered complete cure if he showed disappearance of tumor by imaging after end of his protocol, otherwise, he has the progressive disease and considered relapsed if he has a recurrence of tumor after remission.

Continuous complete remission (CCR) is considered when there is complete disappearance of initial signs and symptoms of the tumor[14 15].

The relapsed patients are treated with MAGRATH protocol, the details of MAGRATH protocol are shown in appendix: 5. The patient was considered lost to follow up if he did not attend for at least 6 weeks from the last visit. Most of the patients received prophylaxes granulocyte colony stimulating factor (GCSF) after each course of chemotherapy to reduce the incidence of febrile neutropenia as a side effect of chemotherapy. Regular follow up after finishing treatment was performed by doing a chest x-ray, ultrasound, CT scan or MRI (if indicated) plus clinical assessment at 2-month intervals during the first year, every 3 months during the 2nd year then 4-6 months intervals up to 5 years. The final outcome of the

patients was assessed for correlation with tumor type , stage and risk group

Statistical Analysis:

Statistical package for social sciences version 24 (SPSS v24) used to analyze data. Continuous variables are presented as means with standard deviation and discrete variables are presented as numbers and percentages. Chi-square to independence is used to test the significance of the association between discrete variables. Kaplan-Meier cohort analysis was used to sketch survival plots. The cure was considered a survival event, and both loss to follow up and death were considered as non-survival events. The significance of survival variation according to studied variables was tested with the log-rank test. Results are considered significant when P value less than 0.05.

The event free survival (EFS) is defined as a measure of a proportion of patients who remain free of a particular event, any event (death, relapse, or loss to follow up) and calculated from the date of diagnosis to the first event. The overall survival (OS) was calculated from the date of diagnosis to death[16 17] .

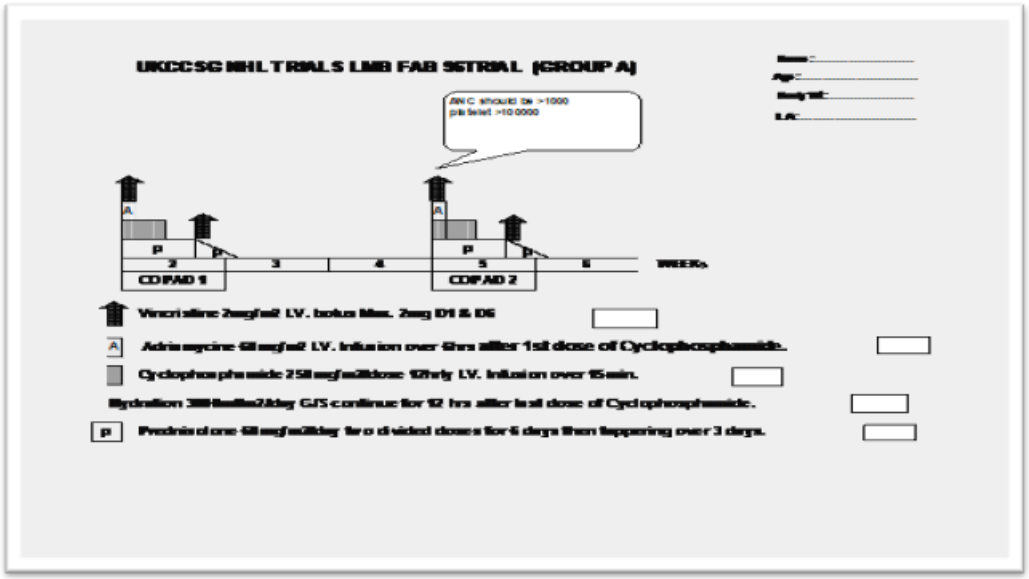

Figure 1 **Mo**dified UKCCSG FAB LMB 96 protocol (United Kingdom Children Cancer Study Group Lymphomes Malins B 96) for children with NHL (group A)

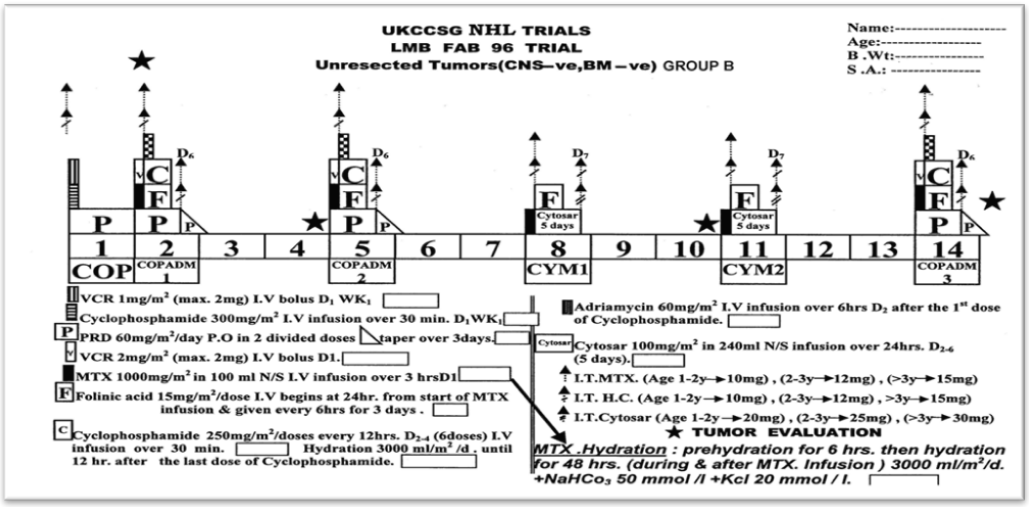

Figure 2 Modified UKCCSG FAB LMB 96 protocol for children with NHL with unresected tumors, CNS -ve, BM -ve (group B)

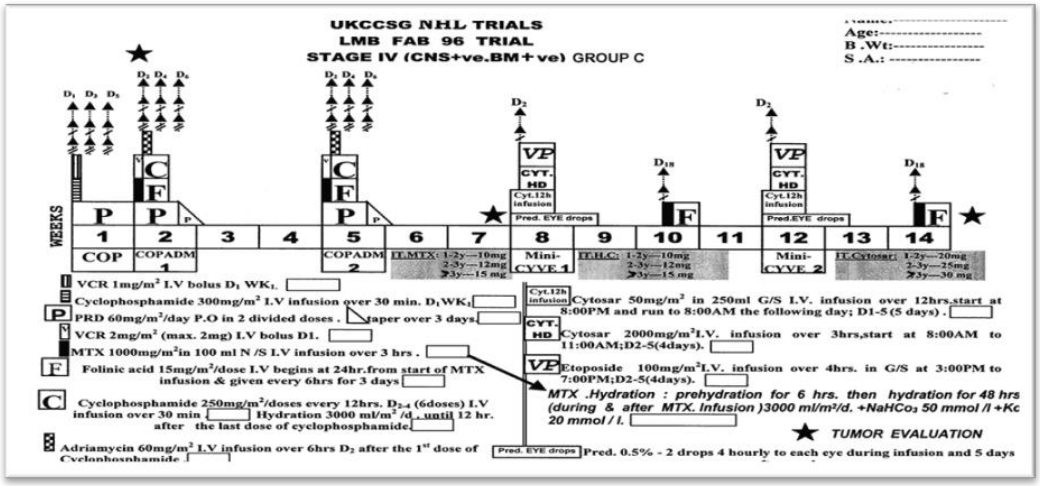

Figure 3 Modified UKCCSG FAB LMB 96 protocol for children with NHL with Stage 4, CNS +ve, BM +ve (group B) *In Group C (CNS –ve), Week 10 omitted

RESULTS

According to the initial Risk group, the most frequent group was group B 92 patients (89.3%), followed by group C 10 patients (9.7%) and group A 1 patient (1%). Sixty-four patients (62.1%) had achieved continuous complete remission after assessment by pediatric oncologist , while 23 (22.3%) patients passed during the course of the treatment. Twelve patients (11.6%) have an evidence of disease relapse or progression during treatment.

Of 12 patients in progressive disease or relapsed patients:

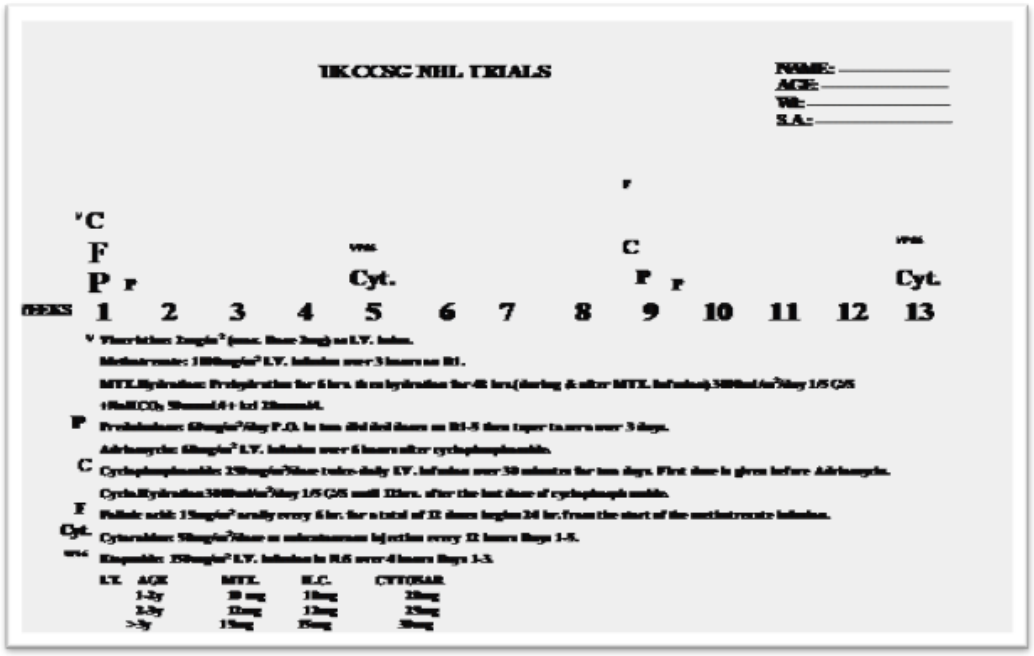

Figure 4 Modified UKCCSG FAB LMB 96 protocol for children with NHL (group C)

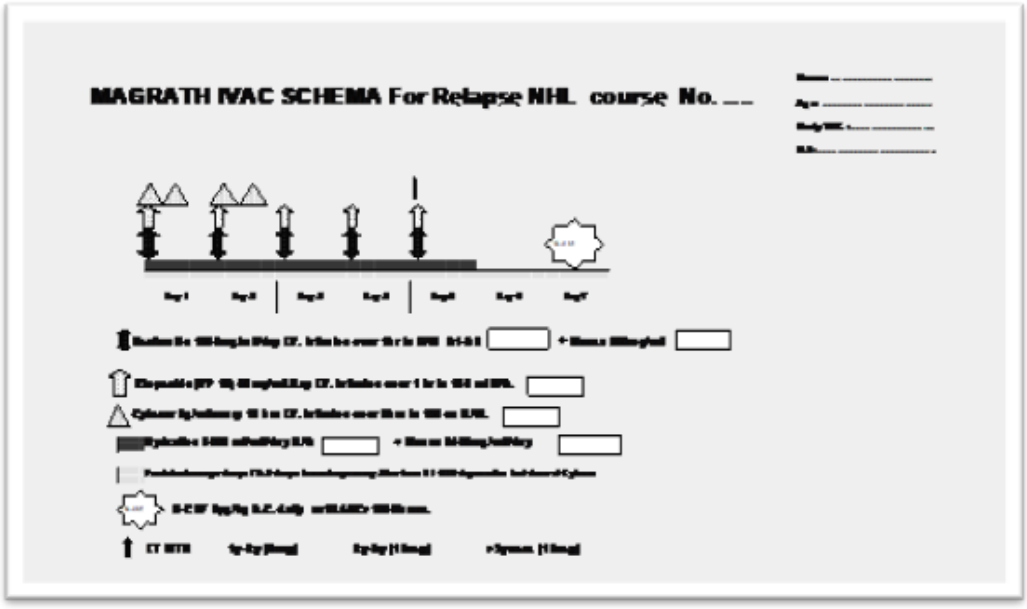

Figure 5 MAGRATH protocol for pediatric patients with relapsed NHL

• One patient achieved remission (patient was treated initially with group C then he considered with progressive disease after complete maintenance and shifted to MAGRATH).

• Four patients died (2 patients were treated initially with group C then shifted to MAGRATH; one of them had progressive disease and died before start of MAGRATH while the other died after the end of MAGRATH with CNS relapse manifestation and the other 2 patients were treated initially with group B but considered progressive disease, shifted to group C; one of them left his treatment for few weeks after COPADM1 and returns back with fit and CNS manifestations then treated with group C protocol and died during treatment, while the other patient had positive tumor evaluation after complete group B protocol, then treated with group C protocol and died during treatment) .

• Seven patients were lost of follow up (patients with group B were considered a progressive disease because they had positive tumor evaluation after end of their protocol and discharge on their responsibility, so considered a loss of follow up).

The final outcome of B cell NHL, 65 patients (63.1%) achieved continuous complete remission (CCR), 27 patients (26.2 %) died, and 11 patients (10.67 %) were lost of follow up, as shown in table 1.

Table 1: Risk group &Outcome of B-cell NHL.

Table 1. **Risk group &Outcome of B-cell NHL.**

Variable	Category	Number	FREQUENCY (%)
Initial Risk Group	Group A	1	1
	Group B	92	89.3
	Group C	10	9.7
Initial Outcome	CCR	64	62.13
	Relapse/Progress	12	11.65
	Death	23	22.34
	Loss of follow up	4	3.88
The outcome of relapse/progress	CCR	1	8.33
	Death	4	33.33
	Loss of follow up	7	58.34
Final outcome	CCR	65	63.10
	Death	27	26.23
	Loss of follow up	11	10.67

CCR: continuous complete remission.

Of the total death (27 patients), eight patients (29.6%) died at 1st cop followed by seven patients (25.9%) who died at COPADM1. Sepsis was the most common cause of death in 14 patients (51.85 %) followed by TLS 6 patients (22.2 %); details are shown in Table 2.

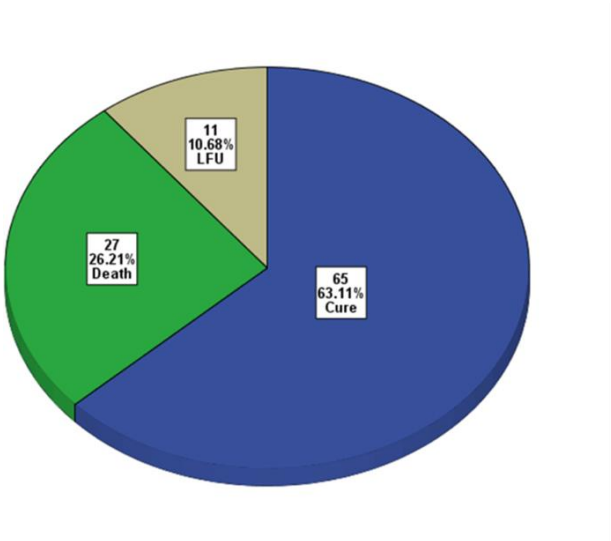

Figure 6 **Figure 6: Final outcome of children with B cell NHL.**

Table 2. Time &Cause of Death of B cell NHL

Time	Frequency (%)	Cause of death
1st cop	8 (29.6)	5 TLS/3 Sepsis
2nd cop	3(11.2)	1 TLS/2 GIT bleeding
COPADM1	7(25.9)	7 Sepsis
COPADM2	5(18.5)	4 Sepsis/ 1 renal failure
Minicyve 1	1(3.7)	Peritoneal dialysis
Minicyve2	1(3.7)	Peritoneal dialysis
Maintenance	1(3.7)	Liver failure
MAGRATH	1(3.7)	CNS relapse

TLS: tumor lysis syndrome, GIT: gastrointestinal tract, CNS: central nervous system.

There was a significant association between final outcomes and histological subtype of B-cell NHL when BL had an excellent continuous complete remission (77.2%) followed by Unclassified NHL (56.7%) ($P < 0.05$).The final outcome was better in stage l and stage II in comparison with stage III and IV (P value =0.038). There was a strong significant association between final outcome and Risk group (P value <0.001) when CCR in group A and B were better than group C, details shown in table NO.3

BL: Burkitt's lymphoma, DLBCL: Difuse large B-cell lymphoma , CCR: continuous complete remission.

Five years event free survival EFS in this study was 59.5% with a mean duration of follow-up 216.4 weeks, as shown in figure 7. Five years overall survival OS was 68.4% with a mean duration of follow up 246 weeks, As shown in figure 8

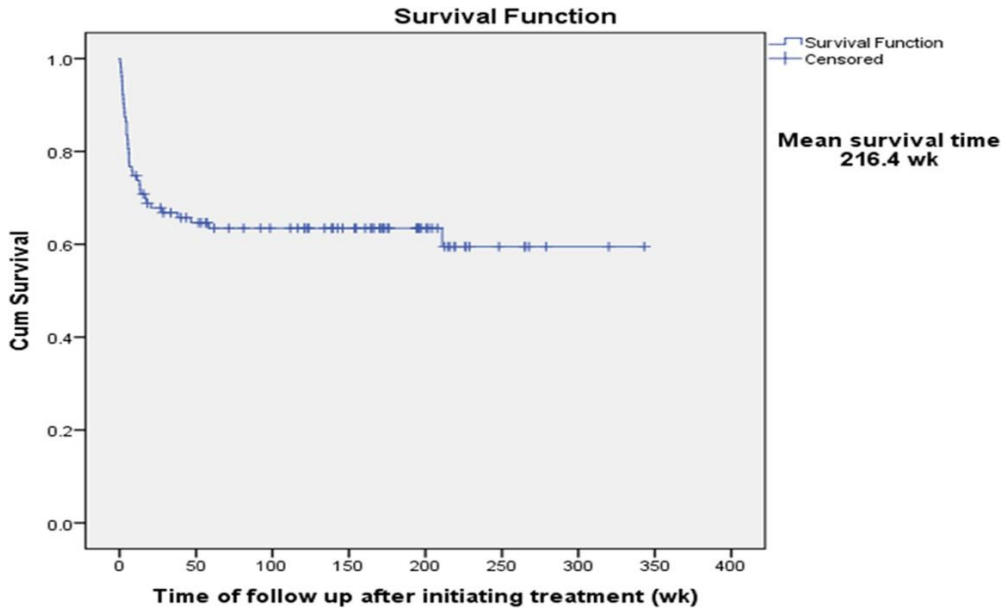

Figure 7 Event-free survival of 103 patients with B cell NHL

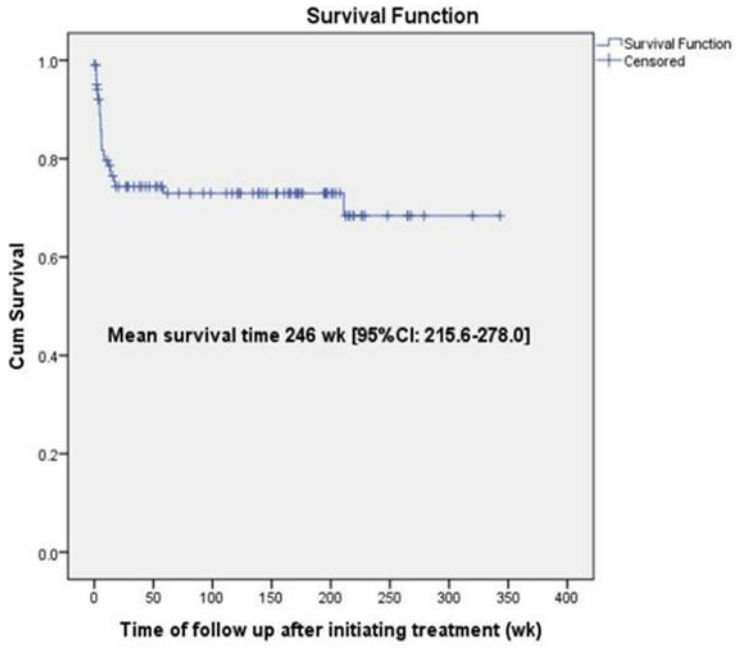

Figure 8 Overall survival of 103 patients with B-cell NHL

Table 3. Correlation between subtype stages &Risk group of B-cell NHL &outcome.

Variables	total	CCR	Death & loss of follow up	
	N=103	N=65	N=38	P value
Subtype				<0.001
BL	57	44(77.2%)	13(22.8%)	
DLBCL	16	4(25.0%)	12(75.0%)	
Unclassified	30	17(56.7%)	13(43.3%)	
Stages				0.038
Stage l	1	1(100.0%)	0(0.0%)	
Stage II	17	16(94.1%)	1(5.9%)	
Stage III	75	47(62.7%)	28(37.3%)	
Stage IV	10	1(10.0%)	9(90.0%)	
Risk Group				<0.001
Group A	1	1(100.0%)	0(0.0%)	
Group B	92	63(68.5%)	29(31.5%)	
Group C	10	1(10.0%)	9(90.0%)	

DISCUSSION AND CONCLUSIONS

Improved event-free survival and overall survival of B-cell NHL in our center as compared with previous studies.

Pediatric patients with B-cell NHL in Iraq are treated in the oncology departments of tertiary hospitals and Central Child Teaching Hospital is one of the largest hospitals dealing with pediatric patients being diagnosed with malignant diseases .Pediatric patients with B-cell NHL receive chemotherapy according to modified UKCCSG LMB-FAB96 protocol and According to this protocol, patients with B-cell NHL in this study were divided into three groups; the smallest percentage of patients were seen in group A where only one patient (1%) treated initially in group A, this percentage is similar to Ibrahim et. al study in Iraq[17] but lower than Pedrosa et al [18] & Cairo et al study in USA [19] within which (9.1% and 12%) treated as group A consecutively. Most of the patients (89.32%) were treated initially as group B, as seen in other studies like; Ibrahim et al. 76.6% [17] , Cairo et al study 66% [19] and Ahmed et al 72.9% [10] .Ten patients (9.71%) were treated initially as group C, which is similar to Faizan et al. 8.4 %[20] but lower than the Cairo et al. study in USA 22%[19] .

In this study, about two thirds of patients (63%) were achieved continuous complete remission which is similar to a study by Faizan et. al. in Pakistan[20] but higher than Ibrahim et al. study in Iraq 29.76% [17] .This could be attributed to improved conditions and better management strategies for children with B-cell NHL in Iraq.

The percentage of death in this study was about (26%) which is nearly similar to other studies by Faizan et al.[20] , Ibrahim et al. study[17] and Christy K in Brazil[21] who found that

the death rates were (21.9%,28.58%, 26% respectively). The loss of follow up in the current study was (10.67%) which is like Faizan et al study [20] but lower than Ibrahim study at Iraq 20.5%[17].

Sepsis was the most common cause of death seen in 51.85% of this study like Ibrahim study in Iraq 41.6% [17] but lower than Ahmad et al study 62.2% [10] . Sepsis is well documented cause of mortality in children with NHL in the pediatric population[22] . TLS was the second most common cause of death in this study seen in about (22%) this is like Ibrahim et al study [17] and Ahmad et al [10]. The high percentage of sepsis as the most common cause of death explained by high rate of bacterial resistance to antibiotics and the limited availability of new generation of antibiotics [23 24 25 26] , antifungal , laboratory investigations (urine and blood culture) and poor hygiene and sanitation in the developing countries as compared to more developed one [27 28 29] . When TLS was the second common cause of death in this study which is explained by the delay of diagnosis, lack of rasburicase and multidisciplinary team to deal with[30 31]

Recent studies from different parts of the world show improved survivals in children with NHL [32 33 34 35] . In this study, event free survival in children with B-cell NHL treated by modified UKCCSG LMB-FAB96 protocol correlate significantly with three factors: the histological subtypes, murphy staging, and treatment protocol. There was a significant correlation between histological subtype and event free survival, BL was correlated with better survival while DLBCL with the worst which was similar to Cairo et al study in USA [19].In this study , there was significant correlation between murphy staging &event free survival similar Cairo et al [19]and in Ahmed N. et al [10] where stage l and II have outcome better than stages III and IV .The probability of event-free survival of NHL patients according to treatment protocol was significant; patients present with group A have excellent survival, and better than group B, while the patients present with group C have the worst survival, this similar to Cairo et al cohort study in the USA [19] and Rehman study in Pakistan[36] .

The 5 years EFS in this study was 59.5% which is near similar to Ahmed N et al 55% [10] but lower than Klumb et al 71% [37] , Guo J et al 74% [38] and Pedrosa et al 68% [18] .In this study, The 5 years OS was 68.4% which is similar that found in Ahmed N et al in Pakistan[10], and Pedrosa et al in Brazil [39] where OS was 68%,70.2% and 70% respectively ,but lower than in Guo J et al in china 79% , Karadeniz et al study in turkey 85% [39] and Cairo et al study in USA91%[19].

Conclusions

Pediatric patients with B-cell NHL who treated by modified UKCCSG FAB LMB 96 protocols display an improved event-free survival and overall survival. The outcome was significantly better in Burkitt's lymphoma and children with tumor stages (I, II, III), and risk group (A). Sepsis and Tumor lysis syndrome were the most common cause of death.

Abbreviations

BL	Burkitt's lymphoma
BM	Bone Marrow
CCR	Continuous Complete Remission
CBC	Complete blood count
CNS	Central Nervous System
DLBCL	Diffuse large B-cell lymphoma
EFS	Event free survival
GCSF	Granulocyte colony stimulating factor
GIT	Gastrointestinal Tract
LDH	Lactate dehydrogenase
NHL	Non-Hodgkin lymphoma
UKCCSG FAB LMB 96	United Kingdom Children Cancer Study Group French-American-British Lymphomes Malins B 96
SFOP	Studies of the French Society of Pediatric Oncology.
TLS	Tumor lysis syndrome

Limitations of the study: the study has a limitation of being a single center study in addition to small sample size so the results cannot be representative to patients in other centers .However it can lead to a large scale multicentric studies **.**

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Conflict of interest: none

Authors contributions: All authors contribute to study design, data collection and approved the final version of the study.

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