Effect of Chemotherapy Related Hyperglycemia on Bone Marrow Response to Induction Treatment in Children with Acute Lymphoblastic Leukemia

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Abstract

background:acute lymphoblastic leukemia (ALL) is a group of hematological neoplasia accounts for 25% of childhood cancers and up to 75% of childhood leukemia. Hyperglycemia is one of common side effects of chemotherapy that affects survival rates in adults, aim of this study is to show the effect of chemotherapy-related hyperglycemia on the response to treatment as remission conditions in children with ALL.

Patients and methods:prospective study carried out in the Clinical Pathology Department ofSohag Oncology Centerand Sohag University Hospital,on total 109 patients in addition to 20 healthy children as control groupthe study depends on measuringrandom blood glucose level before, during and after induction chemotherapy and comparing the response of bone marrow at the end of induction between hyperglycemic patients (random blood glucose ≥200 mg /dl) andeuglycemic patients(random blood glucose within normal values).

Results:patients developed hyperglycemia were 33 (30.3%) while patients with euglycemia were76(69.7%) and according to the remission state after induction chemotherapy, 99 patients (90.8%) had achieved complete remission state while 10 patients (9.2%) had no remission,60%of patients with no remission were hyperglycemic during the induction period, and 26(78,8%) of the 33 hyperglycemic patients aged ≥10years.

Conclusion:hyperglycemia affects the rate of complete remission in ALL children during induction chemotherapy and its incidence ishigher in age group≥10 years old

Introduction

Acute lymphoblastic leukemia (ALL) is a group of hematological neoplasiadefined by cytomorphology, cytochemistry, immunological markers, and more recently, molecular markers***(Munker et al., 2007).***

The incidence of ALL is higher among boys than girls, and this difference is greatest among pubertal children(***Mejia et al., 2013).***The basic components of various therapies for children with ALL are similar and include several discrete phases. Induction therapy lasts 4 to 6 weeks and includes a glucocorticoid (prednisone or dexamethasone), vincristine, an L-asparaginase preparation, optional use of an anthracycline, and intrathecal chemotherapy,after remission, treatment includes 6 to 8 months of intensive combination chemotherapy that is designed to consolidate remission and prevent development of overt CNS leukemia,patients then receive low intensity "antimetabolite"- based maintenance therapy for 18 to 30 months***(Bhatia S, et al 2014).*** About 1

to 2% of children with ALL die before attaining remission, and an additional 1 to 2% die from toxic effects during remission. Chemotherapy-related hyperglycemia is the appearance of random blood glucose ≥200 mg/dl twice or more during the L-asparaginase and dexamethasone-contained inductive chemotherapy **(*Hunger et al. 2015*)**.The potential causes of the hyperglycemia may include beta cell dysfunction caused by chemotherapeutic drugs such as L-asparaginase, increased insulin resistance and hepatic gluconeogenesis induced by corticosteroids, or synergistic effects of these medications, given that these pharmacological agents are usually combined during initial induction therapy***(Howard SC et al 2005).***The combination of L-asp and glucocorticoids, as well as the disease stress, might be the main reason of hyperglycemia (***Vu et al., 2012***)Transient hyperglycemia developed during this period largely resolves as thechemotherapy is discontinued. However, affected children may need longer hospitallization and delay in chemotherapy; they may experience increased infective incidence and may even have poorer survival outcomes. (***Roberson JR et al 2009)***

Objectives:

- Studying the effect of chemotherapy related hyperglycemia on the response to treatment as remission condition after induction chemotherapy in ALL children.

Patients and methods:

Study design: prospective, descriptive study, carried out inClinical Pathology Department of Sohag Oncology Center and Sohag University Hospital on total 109 patients with ALL classified into group I: before induction chemotherapy, group II: after induction chemotherapy, in addition to 20 healthy children as control groupreferred to as group III, then on the 8th day of induction treatment group II was subdivided according to random blood glucose level into: group IIa: with hyperglycemia (random blood glucose ≥200 mg /dl) and group IIb: with euglycemia (random blood glucose within normal values).

Samples: 6 ml venous blood sample is collected on EDTA contained tube for doing complete blood count(CBC) and3 ml venous blood sample on a plain dry tube for blood chemistry. CBCwas performed on the DIAGON D-CELL 60 automated hematology analyzer (DIAGON Hangary 1989), blood chemistry tests (urea, creatinine and random blood sugar) were done by the AU480 chemistry System (Beckman Coulter AU480 Clinical System/2009)USA.

The following parameters are done in this study:

A) Routine investigations:

- Complete blood count (CBC)
-Random blood sugar level.
- Renal function tests: blood urea and serum creatinine.

B) Specific investigations for ALL children:

-Bone marrow aspiration on 15^{th}day and 33^{rd} day of induction treatment.

Every ALL child was performed the blood glucose test on the 8th day and 33rd day of induction treatment twice or more times. If random blood glucose≥200 mg/dl twice or more on 8th day of induction treatment it means hyperglycemia, follow up the patients during the period of induction byCBC on 8th day, 15th day and 33rd day of treatment, and bone marrow aspiration on 15th day and 33rd day of treatment. Urea and creatinine were done again at the end of induction treatment.

Statistical Analyses: All the data were statistically analyzed using SPSS 24.0 software. The risk assignment analysis of hyperglycemia used the X^2 test, Anova test, the CR rate comparison of

the 2 subgroups used the Fisher exact test; the counting data used Chi square test with *P<0.05* considered as the statistical significance

Results of the study:

This study was carried out on 109 children with ALLaged from 1 to 17 years old including 77 males and 32females,in addition to 20 healthy children as a control aged from 1 to 17 years old including 14 males and 6 females during the period from December 2016 to January 2018, in Clinical Pathology Department of Sohag Oncology Center and SohagUniversity Hospital. The 109 patients after starting induction treatment were subdivided according to random blood glucose level on the 8th day of inductioninto group IIa: with hyperglycemia including 33 (30.3%) patients (random blood glucose ≥200 mg /dl) and group IIb: with euglycemia including 76 (69.7%) patients (random blood glucose within normal values).

- We found that hyperglycemia is significant in patients aged ≥10 years as show in table (1)

Age (yr) at diagnosis	Number	Group IIa Hyperglycemia	Group IIb Euglycemia
≥10 years	71	26 (36.6%)	45 (63.4%)
<10 years	38	7 (18.4%)	31 (81.6%)
P value		>0.05	>0.05

Table (1) Age comparison between subgroups

- According to sex there was statistically significant difference between the two subgroups (p value 0.001) as shown in table (2).

		Number (%) N=109	Group IIa Hyperglycemia N=33	Group IIbEuglycemia N=76	P value
Gender	Males	77 (70.6%)	16 (20.7%)	61 (79.3%)	0.001
	Females	32 (29.4%)	17 (53.1%)	15 46.9%)	

Table (2) Gender distribution in Group IIa and Group IIb

- As regarding blood sugar level in the studied groups there was significant relation between group I and group II as shown in table (3)

Parameter	Group I ALL (n=109)	Group II ALL (n=109)	Group III Control (n=20)	P value		
				I versus II	I versus III	II versus III
Random blood sugar(mg/dl) Mean ± S.D Range	96 ± 9.79 77- 117	103.3±12.17 77 - 120	99±10.09 80 -115	<0.05	>0.05	>0.05

Table (3): Random blood sugar in the studied groups

- Also there was significant relation between the two sub groups as shown in tables (4) and (5)and the ratio of patients developed hyperglycemia to euglycemiawas 33 (30.3%) to 76(69.7%)
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Parameter	Group IIa Hyperglycemia (n=33)	Group IIb Euglycemia (n=76)	Group III Control (n=20)	P value		
				$IIav_sIIb$	$IIav_s$ III	$IIbv_s$ III
Random blood sugar (mg/dL) Mean ± S.D Range	287 ± 63.8 217 - 412	105.9 ± 12.8 79 - 143	99±10.09 80 -115	< 0.001	< 0.05	>0.05

Table (4) Random blood sugar between subgroups on 8th day of induction

Parameter	Group IIa Hyperglycemia (n=33)	Group IIb Euglycemia (n=76)	Group III Control (n=20)	P value		
				$IIav_sIIb$	$IIav_s$ III	$IIbv_s$ III
Random blood sugar (mg/dL)						
Mean ± S.D	113.70 ± 6.21	99 ± 11.3	99±10.09	< 0.05	> 0.05	>0.05
Range	100 - 120	79 – 119	80 -115			

table (5) Random blood sugar between subgroups at the end of induction

According to CBC parameters the study showed significant relationship between patients with white blood cell count $\geq 20\times10^9$ /L and patients with white blood cell count $<20\times10^9$/L in group IIa and group IIb at the end of the induction period on the 33rd day with no significance in other CBC parameterson the other hand, peripheral blood juvenile cells at diagnosis were >5%and by comparison between peripheral blood juvenile cells in hyperglycemic and euglycemic cases it showed that there was no significance between the two subgroups on the 8th day of induction treatment but it was significant on 15th day and 33rd day.

Peripheral blood juvenile cells		Number	Group IIa Hyperglycemia	Group IIb Euglycemia	*P* value
8th day	**$<1.0\times10^9$/L**	51	13 (25.5%)	38 (74.5%)	> 0.05
	$\geq1.0\times10^9$/L	58	20 (34.5%)	38 (65.5%)	
15th day	**$<1.0\times10^9$/L**	89	23 (25.8%)	66 (74.2%)	<0.05
	$\geq1.0\times10^9$/L	20	10 (50%)	10 (50%)	
33 day	**$<1.0\times10^9$/L**	99	27 (27.3%)	72 (72.7%)	<0.05
	$\geq1.0\times10^9$/L		6 (60%)	4 (40%)	

Table (6): Conditions of hyperglycemia during the inductive chemotherapy according to peripheral blood cells

• Bone marrow aspiration was done at the diagnosis of the 109 patients with ALL and all showed >30% blast cells in bone marrowand by evaluation of bone marrow during the period of induction there was no significant relationship between bone marrow findings at 15th day between the two subgroups but it was significant at 33th P value < 0.05 as show in table (7)

	Number of immature cells	Group IIa Hyperglycemia	Group IIb Euglycemia	*P* value
BM finding on 15th day	17	4 (23.5%)	13(76.5%)	> 0.05
	31	7 (22.6%)	24 (77.4%)	
	61	22 (36%)	39 (64%)	
BM finding on 33 the day	99	27 (27.3%)	72(94.7%)	< 0.05
	5	2 (40%)	3 (60%)	
	5	4 (80%)	1 (20%)	

Table (7): Conditions of hyperglycemia during the inductive chemotherapy according to bone marrow finding during inductive therapy

As regarding renal function tests we found no significance between the two subgroups

Discussion

Chemotherapy-related hyperglycemia during the L-asp and dexamethasone-contained inductive chemotherapy is defined as the appearance of random blood glucose ≥200 mg/dl twice or more times***(Bochicchio et al., 2010)***. There is a complex pathophysiology mechanism that explains the development of hyperglycemia in the pediatric population receiving

induction chemotherapy ***(Maria et al,2018***)

In this study, a total of 109 children diagnosed as having acute lymphoblastic leukemia in addition to 20 healthy children as a control group were included into the statistics. our patients were aged from 1 - 17 years old, their mean age was 10.26 years, SD 4.43 years similar to the study of **Banihashem et al, (2014)** as patients were children in the range of 1 to 14 years old (mean age was 6.26 years old). Our study showed that there was significant relationship between the age and conditions of hyperglycemia during the inductive chemotherapy as hyperglycemia is significant in age group more than 10 years old. This was similar to results of **Zhang et al. (2014)** as the hyperglycemia incidence≥10-year-old children was significantly higher than the lower age group (43.33% VS 19.23%, P=0.008). A number of studies had confirmed that the age >10-year-old when initially diagnosed was the predilection

age of hyperglycemia during the child ALL inductive remission period, and it was also a risk factor towards the ketoacidosis ***(Gatzioura et al ,2016)***, and thus became the index of poor prognosis in a number of collaborative groups (**Roberson et al., 2008**; **Lowas et al., 2009; Roberson et al., 2009; Sonabend et al., 2009; Spinola-Castro et al., 2009).**

Regarding sex in our study we found that there was a significant difference (P value 0.001) between Group IIa and Group IIb as patients in Group IIa included 16 (20.7%) males and 17(53.1%) females, Patients in Group IIb included 61(79.3%) males and 15 (46.9%) females in contrast to the Study of **Zhang et al (2014**) which included 23 males (19.7%) and 15 (35.7%) females in hyperglycemic group and 94 (80.3%) males and 27 (64.3%) females in euglycemic group with no significant difference (p value 0.056).In our study the ratio of patients whodeveloped hyperglycemia to euglycemia was 33 (30.3%) to 76(69.7%) patients which is close to results of **Weiser et al(2004)** as percentage of children developing hyperglycemia was 37 %,and on the other hand our results were higher than the results reported by**Banihashem et al (2014)** as it was 27.5 % and **Zhang et al. (2014)** that showed, 38 patients (23.90%) out of 159 children occurred the chemotherapy-related hyperglycemia, and 121 patients (76.1%) did not developed the hyperglycemia, thus divided in the euglycemia group.As regarding CBC in our study when we compared between white blood cell count in hyperglycemic and euglycemic cases, we found significant relationship in white blood cell count between group IIa and group IIb on the 33rd day. As regarding random blood sugar at the end of induction treatment, we found that the mean value of blood sugar in group IIa was 113.70, SD was 6.21 and the range was (100 – 120mg/dL) and The mean value of blood sugar in group IIb was 99, SD was 11.3 and the range was (79 - 119 mg/dL) with high significant relation between the two groups.

According to the remission state, we found that there was significant relation between complete remission to no remission as it was 99 (90.8%) to 10 (9.2%) respectively with p value less than 0.05 and 60% of cases with no remission were hyperglycemic during induction therapy. In contrast, **Zhang et al. (2014)** found that there was no significant difference between the hyperglycemic and euglycemic groups (P=0.134) as regards remission state as among the 38 cases of the hyperglycemia group in their study, 33 cases achieved CR (86.8%), while

among the 121 cases of the euglycemia group, 115 cases achieved CR (95%) (**Zhang et al. 2014**).

Conclusion

Hyperglycemia is a common toxicity in patients undergoing treatment for ALL, often due to administration of corticosteroid therapy, but also during treatment with L-asparaginase.This study showed the difference in the rate of complete remission between ALL childrenwho developed hyperglycemia during induction chemotherapy and ALL children who were euglycemic as hyperglycemic cases had complete remission rate less than euglycemic cases (27.3%) to (72.7%) respectively, also it showed a significant difference in hyperglycemic male to female ratio.This study also showed that the risk of developing hyperglycemia in ALL children increases with age as it was more significant in ALL children aged ≥10 at time of diagnosis.

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