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Original Article

Impact of Steroid-Induced Diabetes on Prognosis of Patients with Aggressive Lymphoid Malignancies: A Prospective Study

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Abstract

Background: Hyperglycemia is frequent during steroid therapy and thus it is not uncommon during treatment of lymphoid malignancies. Steroid-induced diabetes (SID) can be complicated by an increased risk of infections, lower chemotherapy efficacy, and even increased mortality.

Aim: To determine the prevalence of SID in patients with aggressive lymphoid malignancies during induction therapy and to analyze its impact on treatment outcomes.

Methods: The study included 52 patients with lymphoid malignancies; 28 with acute lymphoblastic leukemia (ALL) and 24 with aggressive non-Hodgkin's lymphomas (NHL). We studied the relation between the development of SID during induction therapy and the rates of complete remission (CR), complication and relapse and survival.

Results: Steroid-induced diabetes occurred during induction therapy in 18/28 (64%) and 8/24 (33%) patients with ALL and NHL, respectively. Older age and elevated bilirubin level were significantly associated with the development of SID during induction therapy in ALL patients (p = 0.02 and 0.005, respectively), whereas only older age showed a significant association in NHL patients (p = 0.002). Compared with patients who did not develop SID, those with SID had a significantly higher prevalence of febrile neutropenia in the ALL group (p = 0.001) and pneumonia in the NHL group (p = 0.009). Both ALL and NHL patients with SID were significantly less likely to achieve CR and had a significantly worse overall survival.

Conclusion: The results of this study suggest that SID is frequent during induction therapy in patients with lymphoid malignancies and associated with more complications and worse treatment outcomes.

Keywords: Complications, Diabetes, Lymphoid malignancies, Prognosis, Steroids
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Introduction

Steroids are a common element of chemotherapeutic regimens used for treating lymphoid malignancies such as acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphomas (NHL) [1, 2].

Hyperglycemia is frequent during steroid therapy and thus it is not uncommon during the treatment of lymphoid malignancies. The odds ratio for developing new-onset diabetes after glucocorticoid therapy ranged from 1.36 to 2.31 in various studies. Steroid-induced diabetes (SID) often develops because of diminished insulin secretion, increased insulin resistance and exaggerated hepatic glucose output [3]. It can be complicated by an increased risk of infection, prolonged hospitalization, and even increased mortality [4]. In addition, a study suggested that adult ALL patients who experience hyperglycemia during remission induction therapy may be less liable to achieve complete remission (CR) with lower event-free survival [5].

Our aim was to determine the prevalence of SID during the induction therapy for patients with ALL and aggressive NHL and to evaluate its impact on treatment outcome and complications.

Methods

This was a prospective observational study with target accrual of all patients diagnosed with aggressive lymphoid malignancies and attending Department of Medical Oncology, Mansoura University, Egypt, between January 2017 and January 2018 with follow-up period until December 2018. Fifty-two patients were enrolled in this study. Patients with prior history of diabetes before starting chemotherapy were excluded from the study.

We categorized patients into 2 groups. Group I included 28 ALL patients (19 patients with B cell ALL and 9 patients with T cell ALL). These patients were stratified into standard or high risk based on cytogenetics [6]. Patients in this group were treated by either hyper-CVAD or augmented BFM regimens. Group II included 24 patients with aggressive NHL (20 patients with diffuse large B cell lymphoma and 4 patients with primary mediastinal lymphoma). In this group, patients were treated by DA-EPOCH regimen (with rituximab). The steroids used were dexamethasone 40 mg/day on days 1-4 and 11-14 in course I of hyper-CVAD regimen, prednisone 60 mg/m^2 on days 0-27 in augmented BFM, and prednisone 60 mg/m^2 twice daily on days 1-5 in DA-EPOCH.

Fasting plasma glucose (FPG), 2-h postprandial plasma glucose (PPPG; post 75g glucose drink), and A1C values were measured before starting therapy. Fasting plasma glucose and PPPG were then measured weekly during induction therapy and the mean values were recorded. The glycemic state was graded according to the American Diabetes Association (ADA) to normal (FPG < 100 mg/dL and PPPG < 140 mg/dL), prediabetes (FPG = 100 to 125 mg/dL or PPPG = 140 to 199 mg/dL) or diabetes (FPG ≥ 126 mg/dL or PPPG ≥ 200 mg/dL) [7].

The rates of complications during the induction phase, CR, relapse and mortality were recorded.

Statistical analysis

Chi-square or Fisher's exact tests was used to compare categorical variables between groups. Mann–Whitney U test was used to compare abnormally-distributed continuous variables between two groups. Overall survival (OS) was measured from the date of diagnosis to the date of death. Kaplan–Meier method was used for survival analysis. Comparison of survival was performed using the log-rank test. A p value of <0.05 was considered significant.

The statistical analysis of data was done using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 20 (Armonk, NY: IBM Corp.).

Ethical considerations

This study was approved by the Institutional Review Board of Mansoura University, Mansoura, Egypt (IRB number: MS/16.12.25), and conducted in accordance with the 1964 Helsinki declaration and its later amendments.

Written informed consent was obtained from all patients.

Results

Analysis of Group I (ALL) patients

Of the studied 28 ALL patients, 18 (64.3%) developed diabetes during induction therapy, and 5 (17.9%) had prediabetes. To identify possible risk factors associated with the development of SID during induction therapy, we compared the pretreatment clinical and laboratory variables between SID patients and those with normal glycemic state or prediabetes. Only age and bilirubin level significantly associated with the development of SID in univariate analysis (Table 1). None of the other tested parameters, including the treatment regimen, significantly associated with the development of SID.

In the ALL group, grade 3-4 neutropenia occurred in 25/28 (89.3%) patients during induction therapy and febrile neutropenia was documented in 18/28 (64.3%). The prevalence of grade 3-4 neutropenia, febrile neutropenia and staphylococcus infection were significantly higher among patients with SID (Table 2). Regarding other complications, we noted that diarrhea, pneumonia and soft tissue infection were more frequent in SID patients, but the association was not significant.

Regarding the treatment outcome, all (10/10, 100%) normal/prediabetic patients achieved CR compared to only 6/18 (33.3%) of those with SID (p = 0.001). During the follow-up period, 4/10 (40%) of normal/prediabetic patients and 16/18 (88.9%) of SID patients died. The median OS of normal/ prediabetic patients was not reached versus only 2 months in SID patients (p < 0.0001, Figure 1).

Analysis of Group II (NHL) patients

Of the studied 24 NHL patients, 8 (33.3%) developed SID during induction therapy, and 8 (33.3%) had pre-diabetes. Only older age was

significantly associated with the development of SID in univariate analysis (Table 3). No association was found with other pretreatment clinical/laboratory parameters.

Table 1: Comparing pretreatment clinical/ laboratory parameters and treatment regimen between normal/prediabetic patients and those with steroid-induced diabetes in the acute lymphoblastic leukemia group

Parameter	Normal/ prediabetes (*n*=10)	Steroid-induced diabetes (*n* =18)	*p* value
	***n* (%)**	***n* (%)**	
Gender			
Male	5 (50)	10 (55.6)	0.7
Female	5 (50)	8 (44.4)	
WHO Classification			
B-cell ALL	6 (60)	13 (72.2)	0.3
T-cell ALL	4 (40)	5 (27.8)	
Risk stratification			
Standard-risk	6 (60)	8 (44.4)	0.5
High-risk	4 (40)	10 (55.6)	
Organomegally	8 (80)	15 (83.3)	0.8
CNS Involved	0	1 (6.7)	0.4
Treatment Regimen			
Augmented BFM	8 (80)	9 (50)	0.11
Hyper-CVAD	2 (20)	9 (50)	
	Median (range)	**Median (range)**	
Age (years)	29 (18 -39)	43 (18 -70)	0.02
WBCs (x 1000/µL)	24.0 (2 -224)	7.9 (1.6 - 213)	0.34
Platelets (x 1000/µL)	52 (18 -526)	34 (3 -151)	0.09
LDH (U/L)	629 (343 - 2469)	681 (149 - 14549)	0.81
Albumin (gm/dL)	3.8 (2.9 -4.7)	3.4 (2.5 -4)	0.27
Bilirubin (mg/dL)	0.5 (0.2 -0.9)	1.5 (0.2 -2.9)	0.005
Creatinine (mg/dL)	0.9 (0.6 -5.9)	1.0 (0.6 -5.9)	0.51
Baseline FPG (mg/dL)	66 (60 -107)	80 (60 -107)	0.14
Baseline PPPG (mg/dL)	110 (88 - 123)	108 (80 - 130)	0.66
Baseline A1C%	4.3 (4.0 -4.8)	4.5 (4.0 -5.1)	0.19

ALL: Acute lymphoblastic leukemia, **WHO**: World Health Organization, **CNS**: Central nervous system, **WBCs**: White blood cells, **LDH**: Lactate dehydrogenase, **FPG**: Fasting plasma glucose, **PPPG**: 2-h postprandial plasma glucose

Table 2: Comparing complications between normal/ prediabetic patients and those with steroid-induced diabetes in the acute lymphoblastic leukemia group

Complication	Normal/ prediabetes (*n*=10)	Steroid-induced diabetes (*n* =18)	*p* value
Grade 3-4 neutropenia	7 (70)	18 (100)	0.01
Febrile neutropenia	1 (10)	17 (94.4)	0.001
Staphylococcus infection	1 (10)	16 (88.9)	0.0001
Mucositis	2 (20)	3 (16.7)	0.1
Diarrhea	1 (10)	3 (16.7)	0.2
Pneumonia	0	2 (11.1)	0.1
Skin and Soft Tissue Infections	0	3 (16.7)	0.1

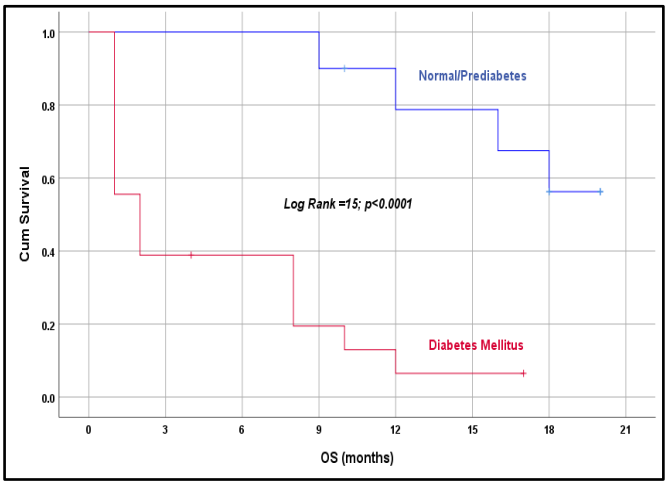

Figure 1: Overall survival curves for normal/ prediabetic patients and those with steroid-induced diabetes in the acute lymphoblastic leukemia group

In this group, 15/24 (62.5%) patients developed grade 3-4 neutropenia with febrile neutropenia reported in 9/24 (37.5%). In contrast to ALL patients, NHL cases showed no significant association between development of SID and the occurrence of febrile neutropenia. In addition, no significant relationship was found with the occurrence of mucositis, diarrhea and soft tissue infections. On the other hand, there was a significant association between SID and the development of pneumonia (Table 5).

Similar to the findings in ALL patients, that majority (15/16, 93.8%) of normal / prediabetic NHL patients achieved CR while 4/8 (50%) of SID patients achieved it (p = 0.01).

Table 3: Comparing pretreatment clinical/ laboratory parameters between normal/ prediabetic patients and those with steroid-induced diabetes in the non-Hodgkin's lymphoma group

Parameter	Normal/ prediabetes (*n*=16)	Steroid-induced diabetes (*n* =8)	*p* value
	***n* (%)**	***n* (%)**	
Gender			
Male	9 (56.3)	5 (62.5)	0.7
Female	7 (43.8)	3 (37.5)	
Ann Arbor stage			
Stage I, II	5 (31.2)	3 (37.5)	0.3
Stage III, IV	11 (68.8)	5 (62.5)	
Extranodal disease	10 (62.5)	5 (62.5)	1
	Median (range)	**Median (range)**	
Age (years)	44 (21 - 54)	56 (45 - 66)	0.002
ESR (mm/hr)	19 (3 - 60)	40 (10 - 60)	0.08
LDH (U/L)	588 (225 - 1979)	707 (354 - 904)	0.95
Albumin (gm/dL)	3.5 (3.0 - 4.4)	3.8 (2.7 - 4)	0.66
Bilirubin (mg/dL)	0.7 (0.2 - 1.1)	0.6 (0.5 - 1)	0.59
Creatinine (mg/dL)	0.9 (0.7 - 1.4)	1.0 (0.7 - 1.1)	0.41
Baseline FPG (mg/dL)	80 (64 - 108)	81 (60 - 100)	0.99
Baseline PPPG (mg/dL)	122 (93 - 132)	110 (94 - 130)	0.25
Baseline A1C%	4.4 (4 - 5)	4.8 (4 - 5.2)	0.31

ESR: Erythrocyte sedimentation rate, **LDH**: Lactate dehydrogenase, **FPG**: Fasting plasma glucose, **PPPG**: 2-h postprandial plasma glucose

During the follow-up period, no relapse was documented and 1/16 (6.3%) normal / prediabetic and 4/8 (50%) SID patients died. The median OS was 7 months in SID patients versus not reached in normal / prediabetics (p = 0.01, Figure 2).

Discussion

Steroid induced hyperglycemia, which is quite common in patients treated for hematological malignancies, may increase the risk of infection leading to prolonged hospital stays or frequent emergency room visits. In addition, steroid induced hyperglycemia may have a harmful effect on patient prognosis according to several retrospective studies [5, 8-10]. To the best of our knowledge, this is the first prospective study to assess the prevalence of SID in patients with aggressive lymphoid malignancies during induction therapy and to assess its impact on the treatment outcome.

The prevalence of SID among ALL patients in our study (64.3%) was higher than that reported by Weiser et al [5] who conducted a study on adult ALL patients managed by HyperCVAD regimen and reported a 37% prevalence of hyperglycemia. In their study, they defined hyperglycemia as random

Table 4: Comparing complications between normal/ prediabetic patients and those with steroid-induced diabetes in the non-Hodgkin's lymphoma group

Complication	Normal/ prediabetes (*n*=16)	Steroid-induced diabetes (*n* =8)	*p* value
Grade 3-4 Neutropenia	11 (68.8)	4 (50)	0.3
Febrile neutropenia	7 (43.8)	2 (25)	0.3
Staphylococcus infection	6 (37.5)	2 (25)	0.5
Grade 3-4 mucositis	4 (25)	1 (12.5)	0.4
Diarrhea	1 (6.3)	2 (25)	0.3
Pneumonia	0	3 (37.5)	0.009
Skin and Soft Tissue Infections	5 (31.3)	2 (25)	0.7

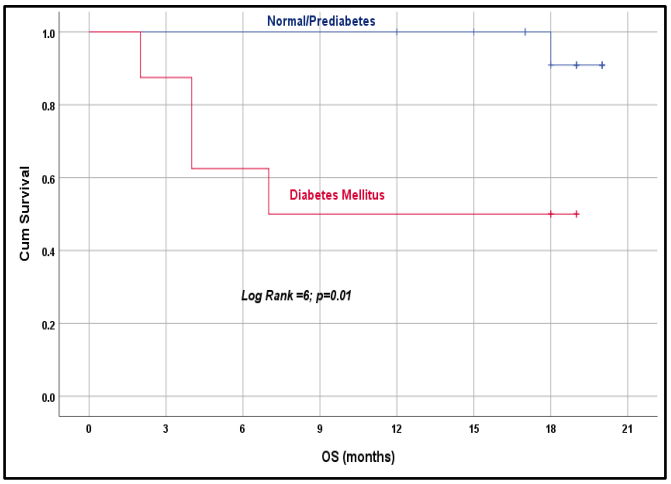

Figure 2: Overall survival curves for normal/ prediabetic patients and those with steroid-induced diabetes in the non-Hodgkin's lymphoma group

blood sugar ≥ 200 mg/dL. In another report by Sonabend et al [9] on hyperglycemia in childhood ALL, the prevalence was 56%. They defined hyperglycemia as mild if the plasma glucose level was 140 - 199 mg/dL and overt if ≥ 200 mg/dL. Variations in genetic and environmental factors between different patient populations may be responsible for these differences in the prevalence observed across studies.

In our study, the median age of patients with SID was 43 years in the ALL group and 56 in the NHL one which was significantly higher than those who did not develop SID in both groups. This finding is consistent with that of Weiser et al [5]. The higher incidence of type 2 diabetes and impaired glucose tolerance in older population can be explained by the progressive decline in glucose tolerance with age. This may result in higher liability to develop diabetes when treated with steroids [11].

In this study, basal bilirubin level was significantly higher in patients with ALL who developed SID. A study investigating two independent cohorts of middle-aged and elderly Chinese adults reported that elevated serum bilirubin was associated with an increased risk of type 2 diabetes independent of other diabetes risk factors [12]. The elevated bilirubin may indicate hepatocellular injury. It has been proposed that reduced insulin elimination by the damaged liver results in hyper-insulinemia that in turn leads to raised levels of anti-insulin hormones (glucagon, growth hormone, insulin-like growth factor, free fatty acids and cytokines) causing glucose intolerance [13].

We observed that the prevalence of grade 3-4 neutropenia was higher in patients with SID than normal/prediabetics. Hyperglycemia and diabetes cause metabolic disorders and changes in the processes of energy production, which is necessary for the generation of neutrophils. Therefore, it is proposed that hyperglycemia may increase the risk of chemotherapy-induced neutropenia [14]. However, since hyperglycemia and diabetes are previously unrecognized as risk factors for chemotherapy-induced neutropenia, the collective evidence of their effect on developing chemotherapy-induced neutropenia during chemotherapy among patients with cancer needs further confirmation [15, 16].

Diabetics in our study developed febrile neutropenia and infections more frequently than non-diabetics, which is consistent with earlier reports [5, 9]. Several explanations underlie the higher infection rate among diabetics. Diabetes adversely impairs neutrophil activity, including chemotaxis, formation of reactive oxygen species and phagocytosis of bacteria [16]. It also affects other components of the immune system, stimulating lymphocyte apoptosis and inhibiting the proliferation of T cells due to the decreased expression of adenosine kinase. In addition, the function of immunoglobulins and complement is attenuated due to their glycosylation in the hyperglycemic environment [17].

The data on disease outcomes of patients who develop diabetes during chemotherapy have been both limited and controversial. Our results have shown that in both ALL and NHL patients, the CR rate was significantly higher in non-diabetics versus those with SID. These results contradict what have been reported in previous studies in which there was no significant difference in CR rate between those who did and did not develop chemotherapy-related hyperglycemia [8, 10]. Various pre-clinical data indicate lower chemotherapy efficacy in hyperglycemic states, which supports our results. First, hyperglycemia can attenuate the anti-proliferative effect of chemotherapy through interference with apoptotic signaling [18]. Second, glucose level can impact chemotherapy efficacy through interference with chemotherapy pharmacokinetics; thus, changing the exposure of cancer microenvironment to chemotherapy [19, 20]. Moreover, studies have found that under hyperglycemic conditions, there is increased expression of various kinases regulating many cellular processes, including growth and proliferation of cancer cells [21].

In the present study, the median OS was significantly longer in non-diabetics vs. diabetics in both ALL and NHL groups. These data are in accordance with those published by Weiser et al [5] who showed that the median survival was 88 months for the euglycemic group versus 29 months for the hyperglycemic one ($p < 0.001$). Similarly, in pediatric patients, few studies have reported worse outcomes in patients who develop hyperglycemia during induction therapy [8, 9]. In contrast, Roberson et al studied the clinical consequences of hyperglycemia during induction therapy for pediatric ALL and found no significant difference in OS, event-free survival, or the cumulative incidence of relapse in association with hyperglycemia [10]. They attributed the difference in results between adults and children to significant variability in dexamethasone pharmacokinetics and higher incidence of co-morbidities in adults, which puts

them at higher risk of multi-organ dysfunction during induction therapy.

In contrast to previous studies, the main strength of our study is its prospective design, which helps in avoiding some statistical bias associated with retrospective analyses. In addition, treatment was standardized for our patients, which allowed for accurate comparison of outcomes based on glycemic state. Our study had limitations. First, this was a single institution study with a relatively small number of patients; a larger study should be carried out in the future to reach firm conclusions. Second, a longer follow-up period is needed to confirm the survival difference detected in our study.

We conclude from our study that SID in patients with lymphoid malignancies is associated with more therapy-related complications and confers worse disease outcomes. Thus, we recommend close monitoring of the glycemic status in patients with lymphoid malignancies receiving induction therapy. It is still controversial whether strict glycemic control should be attempted in this group of patients or not. A study by Vu et al [22] showed that an intensive insulin regimen did not improve ALL outcomes in hyperglycemic patients, while metformin and thiazolidinediones may be associated with improved outcomes. Further research must establish the ideal range for glycemic control in patients with lymphoid malignancies without preexisting diabetes and also to explore strategies to prevent hyperglycemia without affecting response rates or survival.

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Authors' contribution

Conception or design: MAS, MAE; Acquisition, analysis or interpretation of data: ASO, SMA, AMR; Drafting the manuscript: ASO, SMA; Revising the manuscript: MAS, MAE, AMR; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose

Data availability

Deidentified individual participant data used to produce the results of this study are available from the corresponding author (AMR) upon request.

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Study registration

None.

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