Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.jzus.zju.edu.cn; www.springerlink.com
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Characteristics of chemotherapy-induced diabetes mellitus in acute lymphoblastic leukemia patients*#

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https://doi.org/10.1631/jzus.B1900719

Acute lymphocytic leukemia (ALL) is one of the most common malignancies, especially in young people. Combination chemotherapy for ALL typically includes corticosteroids (Kantarjian et al., 2000). Hyperglycemia is a well-recognized complication of corticosteroids, and chemotherapy-induced diabetes (CID) is not uncommon (27.5%–37.0%) during the treatment of ALL (Hsu et al., 2002; Weiser et al., 2004; Alves et al., 2007). Besides the effect of corticosteroids, potential factors triggering hyperglycemia in ALL also include direct infiltration of the pancreas by leukemia cells and β cell dysfunction induced by chemotherapeutic agents such as L-asparagine (Mohn et al., 2004).

Several studies have noted alteration in glucose metabolism during the treatment of ALL (Koltin et al., 2012; Gifford et al., 2013; Banihashem et al., 2014), but few studies have investigated the clinical significance of CID. Weiser et al. (2004) reported that patients with hyperglycemia (37%) had a shorter median complete remission duration and a shorter median survival. However, their study focused on selected populations (patients treated with the hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) regimen). Since patients using the Hyper-CVAD regimen represent only a small part of the patient population in clinical setting, it is not clear whether the prognostic value of CID has a rationale in all ALL patients. To further address this issue, we retrospectively investigated an unselected ALL population with several treatment regimens. We focused on an assessment of its characteristics, risk factors, and its prognostic value on survival.

We collected data from 177 patients with newly diagnosed ALL in the database of the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China) from January 2011 to October 2013. Twelve patients who were treated at other institutions after being initially diagnosed in our hospital and were then lost to follow-up were excluded. A total of 165 patients had completed medical records. Among them, three patients had diabetes mellitus previously and six patients were newly diagnosed as having diabetes mellitus before induction chemotherapy. These patients were not included in the analysis. The remaining 156 patients were included in the current analysis.

The results were statistically analyzed using SPSS statistical software version 20.0 (SPSS Inc., Chicago, IL, USA). The Chi-square test or Fisher's exact test was used to compare categorical variables. Student's *t*-tests and Mann-Whitney *U*-test were used to compare continuous variables. Survival analysis was assessed using the Kaplan-Meier method. All *P*

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* Project supported by the Zhejiang Provincial Natural Science Foundation of China (No. LY19H080009)
# Electronic supplementary materials: The online version of this article (https://doi.org/10.1631/jzus.B1900719) contains supplementary materials, which are available to authorized users
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values were two-sided, with a P value of <0.05 indicating statistical significance.

Of the 156 subjects included, 87 (55.8%) were male. The median follow-up period was 24.7 months (range 0.5–48.3 months), and the median age at diagnosis was 34.5 years (range 15.0–73.0 years). In 118 patients (75.6%) ALL originated from B-cell precursor cells, while in 30 patients (19.2%) ALL originated from T cell or natural killer (NK)-T cell precursor cells. Breakpoint cluster region-Abelson (*BCR-ABL*) fusion gene transcript was detected in 46 patients (29.5%). All 156 patients received VP (vincristine+prednisone)-based induction chemotherapy. Two thirds (111 patients, 71.2%) received the VDCP (or VICP) regimen, which includes vincristine, daunorubicin (or idarubicin), cyclophosphamide, and prednisone. Fifteen patients (9.6%) used L-asparaginase in addition to the VDCP regimen. Fourteen patients (9.0%) underwent the Hyper-CVAD regimen which is comprised of cyclophosphamide twice daily on Days 1–3, doxorubicin on Day 4, vincristine on Days 4 and 11, and dexamethasone on Days 1–4 and 11–14.

Since all patients had fasting glucose level measurements as part of routine blood work two times a week during their hospital admission in our center, hyperglycemia in this study was defined using fasting glucose levels. Patients with a plasma fasting glucose level greater than or equal to 7.0 mmol/L during two or more continuous determinations were defined as having CID. This is in accordance with the American Diabetes Association (2018) definition. Thirty-three patients (21.2%) met the criteria of hyperglycemia during chemotherapy. Of them, 24 patients experienced transient hyperglycemia (lasting one or two chemotherapy cycles and then they recovered) and 9 patients developed persistent hyperglycemia. Seventeen patients (51.5%) were diagnosed with hyperglycemia during induction chemotherapy and the others in following chemotherapies. The median number of chemotherapy cycles developing hyperglycemia was 2.82.

Baseline characteristics according to hyperglycemia status are shown in Table S1. The two groups with or without hyperglycemia did not differ with respect to sex, incidence of hypertension, body mass index (BMI), immunophenotype, or the induction chemotherapy regimen. However, patients in the CID group were significantly older (median age 44 years vs. 31 years, P=0.017).

We then analyzed associations between CID and characteristics such as age, sex, BMI, hypertension, low-density lipoprotein (LDL), triglyceride (TG), and immunophenotype (Table 1). Among the factors selected, univariate analysis showed that CID was significantly influenced by age (P=0.031). Characteristics with P<0.5 were selected into the multivariate analysis. In the multivariate analysis, age greater than or equal to 35 years was significantly associated with the development of CID (P=0.026).

Next, we assessed the prognosis value of CID in ALL patients. In order to eliminate the confounding effect of age on prognosis analysis, we divided all the patients into two groups. The first group was

Table 1 Risk factors of chemotherapy-induced diabetes (logistic analysis)

Variable	Univariate	Multivariate	
	P value	HR (95% CI)	*P* value
Sex (male vs. female)	0.343		0.830
Age (≥35 years vs. <35 years)	0.031	2.824 (1.133–7.034)	0.026
Hypertension (yes vs. no)	1.000		
WBC (>30×10^9 L^{-1} vs. ≤30×10^9 L^{-1})	0.615		
HB (≥90 g/L vs. <90 g/L)	0.839		
PLT (≥100×10^9 L^{-1} vs. <100×10^9 L^{-1})	0.571		
BMI (≥25 kg/m^2 vs. <25 kg/m^2)	0.155		0.333
LDL (>3.29 mmol/L vs. ≤3.29 mmol/L)	0.679		
TG (>1.70 mmol/L vs. ≤1.70 mmol/L)	0.482		0.801
Fusion gene (*BCR-ABL*$^+$ vs. *BCR-ABL*$^-$)	0.588		
Immunophenotype (B vs. non-B)	0.117		0.707
Induction chemotherapy	0.189		0.318

WBC, white blood cell; HB, hemoglobin; PLT, platelet; BMI, body mass index; LDL, low-density lipoprotein; TG, triglyceride; *BCR-ABL*, breakpoint cluster region-Abelson; HR, hazard ratio; CI, confidence interval

comprised of those younger than 35 years and the second of the rest. Table S2 shows both demographic characteristics and a comparison of patients between the hyperglycemia and the normal blood glucose subgroups organized separately into young adult patients and older ALL patients. In both the young adult patients and the older patients, there were no differences with respect to age, gender, incidence of hypertension, BMI, immunophenotype, or the induction chemotherapy regimen between the hyperglycemia and the normal blood glucose subgroups.

Survival results from the young adult patient group are shown in Fig. 1. Patients with hyperglycemia were found to have a shorter median overall survival (OS, 11.3 months vs. > 48.0 months; P=0.002) and a shorter median event-free survival (EFS, 9.1 months vs. 15.9 months; P=0.005). Outcomes for older adult ALL patients are shown in Fig. 2. Using Kaplan-Meier analysis, the median OS was found to be 8.7 months for the hyperglycemia group and 11.8 months for the normal blood glucose group (P=0.989, Fig. 2a). The median EFS rates were 5.7 months and 6.4 months, respectively (P=0.635, Fig. 2b). There was no significant difference between the two groups in terms of OS and EFS in older adult patients.

A number of studies have noted disorders of glucose metabolism during the treatment of ALL (Mohn et al., 2004; Koltin et al., 2012; Gifford et al., 2013; Banihashem et al., 2014). However, the impact of CID on ALL patients is not yet well established. In this study, we demonstrate for the first time the negative impact of hyperglycemia on outcomes for young adult ALL patients. Interestingly, there were no differences among older adult patients. Weiser et al. (2004) found that patients with hyperglycemia during induction chemotherapy had a shorter median complete remission duration (P<0.001) and a shorter median survival (P<0.001). However, the authors did not further analyze the hybrid effect of age, which is an independent negative prognostic factor for both hyperglycemia and ALL (Giovannucci et al., 2010). To eliminate the confounding effect of age, we conducted stratified analysis by classifying age into two groups and we found that an age of 35 years was the best cutoff according to receiver operating characteristic (ROC) analysis. This result still needs validation in other independent cohorts of ALL patients.

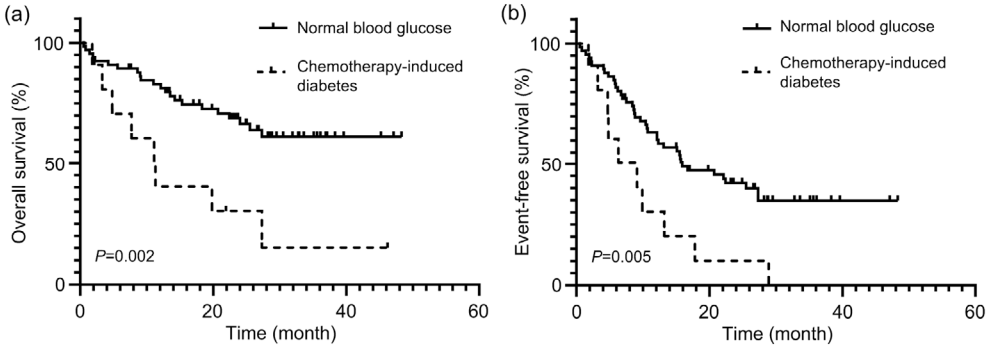

Fig. 1 Kaplan-Meier estimates of overall survival (a) and event-free survival (b) in young adult patients

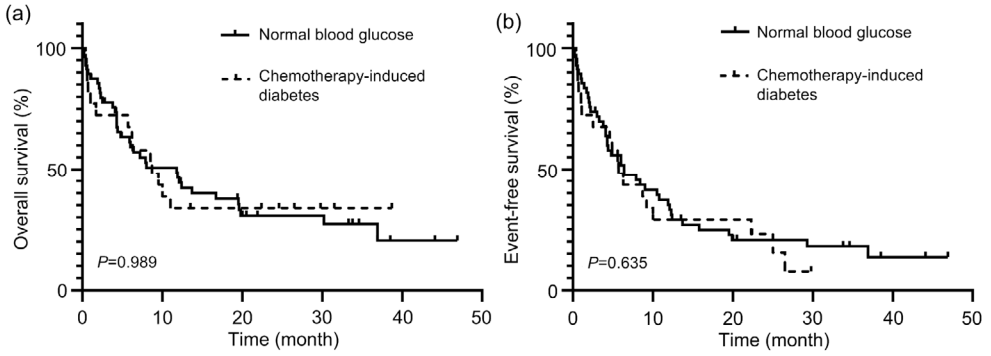

Fig. 2 Kaplan-Meier estimates of overall survival (a) and event-free survival (b) in older adult patients

The relation between CID and poor outcomes in ALL patients is multifactorial. One important factor may be associated with the increased incidence of infection during intensive chemotherapy. Weiser et al. (2004) showed that patients who developed hyperglycemia during induction chemotherapy for ALL were more likely to develop sepsis (P=0.03) or complicated infections (P=0.016) compared with patients without hyperglycemia. On the other hand, hyperinsulinemia, hyperglycemia, and inflammatory cytokines have been shown to be a direct link between diabetes and cancer, which promote the neoplastic process. All these complex factors lead to poor clinical outcomes in CID patients (Giovannucci et al., 2010). Abnormal glucose metabolism may also play a critical role. Studies have shown that acute myeloid leukemia (AML) patients present an altered glucose metabolism signature with poor clinical outcomes (Wang et al., 2013; Chen et al., 2014). Glucose metabolism may also be abnormal in ALL patients, especially CID patients, which would further affect the prognosis of the patients. More research is needed to confirm this.

We also studied the management of hyperglycemia in these CID patients. However, in our study, only eight CID patients (8/33, 24.2%) received glucose-lowing treatments. All these eight patients had undergone insulin therapy and none took oral hypoglycemic drugs, such as metformin or sulfonylureas. Since only one patient in the younger group received treatment for diabetes, we could not analyze whether glucose-lowering treatments could improve the prognosis for these CID patients, which is a limitation of this study. It should be noted that metformin, a widely used anti-diabetic drug, has recently attracted strong interest as a possible new anti-cancer molecule (Rosilio et al., 2013; Zi et al., 2015; Biondani and Peyron, 2018). Rosilio et al. (2013) have reported that metformin could interfere with the growth and survival of human T-ALL cancer cells, and it potentiates the anti-leukemia effects of dexamethasone. Additionally, differences in gut microbial composition were found between ALL children and healthy controls before, during, and even after cessation of chemotherapy (Chua et al., 2020; Thomas et al., 2020). Metformin has been found to benefit microbiota composition, promote gut barrier integrity, and improve metabolic function, which may have a role in the long-term wellbeing in ALL survivors (Ouyang et al., 2020a, 2020b). All these studies showed that metformin may play a unique role as a glucose-lowing therapy in CID patients. Further studies are needed to explore the value of glucose-lowering treatments, especially metformin, in CID patients.

Collectively, our results show that CID is not uncommon in ALL patients and age is an independent prognostic factor for CID development. Furthermore, we demonstrate that CID is an independent prognostic factor for inferior survival in young adult ALL patients.

Contributors

Jie JIN contributed to the conception and design of the study and provided administrative support. Shan-shan SUO, Chen-ying LI, Yi ZHANG, and Wen-juan YU participated in the collection and assembly of data. Shan-shan SUO and Yin-jun LOU performed data analysis and interpretation. Shan-shan SUO and Jing-han WANG were involved in the writing of the manuscript. All authors gave final approval of the manuscript for publication, and have full access to all the data in the study and take responsibility for the integrity and security of the data.

Acknowledgments

The authors wish to thank all the medical and nursing staff working in the Department of Hematology, the First Affiliated Hospital, Zhejiang University School of Medicine (Hangzhou, China) for providing outstanding clinical care to our patients.

Compliance with ethics guidelines

Shan-shan SUO, Chen-ying LI, Yi ZHANG, Jing-han WANG, Yin-jun LOU, Wen-juan YU, and Jie JIN declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. The present study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine (Reference Number 2013-277).

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List of electronic supplementary materials

Table S1 Baseline characteristics by hyperglycemia status of 156 patients studied

Table S2 Baseline characteristics by hyperglycemia status in patients aged <35 years and ≥35 years

中文概要

题　目：急性淋巴细胞白血病化疗继发糖尿病的临床特点

目　的：明确急性淋巴细胞白血病（ALL）患者化疗期间继发糖尿病的发生率，探索发生继发糖尿病的危险因素及其对患者预后的影响。

创新点：继发糖尿病在 ALL 患者化疗期间常有发生，但其在不同化疗阶段的发生率、危险因素及其对患者预后的影响鲜有研究。本研究以此为切入点，探索了 ALL 患者化疗继发糖尿病的特点及其对患者预后的影响。

方　法：收集浙江大学医学院附属第一医院血液科 2011 年 1 月至 2013 年 10 月期间收治的初发 ALL 病例共计 177 例，筛选出临床资料完整且入院时不合并糖尿病的患者 156 例。统计患者在诱导化疗期间和全化疗期间继发糖尿病的发生率，分析糖尿病组与非糖尿病组患者在总生存期、无事件生存期等方面的差异，并探讨继发糖尿病的危险因素。

结　论：继发糖尿病是 ALL 患者化疗期间重要的并发症，年龄是化疗期间继发糖尿病的独立预测因子。对于年龄小于 35 岁的年轻患者，继发糖尿病患者相比于正常血糖者其总生存期和无事件生存期均缩短。

关键词：糖尿病；急性淋巴细胞白血病；临床特点