

RESEARCH ARTICLE

Impact of Chemotherapy-Related Hyperglycemia on Prognosis of Child Acute Lymphocytic Leukemia

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Abstract

Purpose: To investigate the impact of hyperglycemia during inductive treatment on the prognosis of acute lymphocytic leukemia (ALL) in children. **Materials and Methods:** Clinical data of 159 ALL childhood cases were reviewed. The patients were divided into the hyperglycemia group (fasting glucose ≥ 126 mg/dl and/or random blood glucose ≥ 200 mg/dl) and the euglycemia group according to the blood glucose values. The X2 test was performed to compare the complete remission rates of the two groups, and Kaplan-Meier and log-rank tests were performed to compare the 5-year overall and relapse-free survival. **Results:** The incidence of hyperglycemia in the age ≥ 10 -year-old group was higher than the younger-age group ($P=0.009$). Values in the interim- and high-risk groups were higher than the standard-risk group ($P=0.028$), while there was no significant difference between genders ($P=0.056$). The complete remission rates of the 2 groups demonstrated no significant difference ($P=0.134$), while the 5-year OS of the hyperglycemia group was lower than in the euglycemia group ($83.8 \pm 6.0\%$ vs $94.9 \pm 2.4\%$, $P=0.014$). The 5-year RFS was significantly lower than the euglycemia group ($62.9 \pm 8.7\%$ vs $80.2 \pm 9.1\%$, $P < 0.001$). **Conclusions:** Children with age ≥ 10 years old, and in the middle- and high-risk groups appear prone to complicating hyperglycemia during inductive chemotherapy, associated with lower 5-year OS and RFS.

Keywords: Childhood ALL - chemotherapy-related hyperglycemia - relapse-free rate - overall survival

Asian Pac J Cancer Prev, 15 (20), 8855-8859

Introduction

The acute lymphoblastic leukemia (ALL) is the malignant tumor with the highest incidence in the childhood, although the risk-stratification chemotherapy has significantly improved the prognosis, the event-free survival (EFS) and overall survival (OS) have been significantly improved, the recurrence and disease progression, as well as the drug toxicity-related mortality, are still increasing (Hunger et al., 2012). The recent studies have found that during the child critical disease process, the incidence of hyperglycemia was one of the risk factors that would affect the prognosis (Devos and Preiser, 2004; Faustino and Apkon, 2005), and the similar conclusion had been confirmed in the adult malignancies (Ali et al., 2007), the hyperglycemia might directly affect the cell growth, and induce the drug resistance of tumor cells (Feng et al., 2011).

The occurrence of hyperglycemia during the period of inductive remission chemotherapy is an independent risk factor towards the early recurrence and high mortality of adult ALL patients, compared with the non-hyperglycemic patients, the risks were 1.57 times and 1.71 times, respectively (Weiser et al., 2004). because

the L-asparaginase (L-asp) and glucocorticoids are the commonly used drugs during the child ALL inductive chemotherapy, which would affect the production, release and functions of insulin, the chemotherapy-related hyperglycemia is also a common complication of child ALL, with the occurring rate as 4% to 20%, or even as high as 56% (Belgaumi et al., 2003; Sonabend et al., 2008). Currently, the report about the impacts of hyperglycemia during the inductive chemotherapy towards the prognosis of child ALL is few, and the conclusions are inconsistent. This study compares the rates of complete remission, 5-year recurrence-free survival and 5-year overall survival between the hyperglycemic ALL children and the non-hyperglycemic ALL children during the inductive chemotherapy, aiming to analyze the relationship of hyperglycemia and prognosis of child ALL.

Materials and Methods

Study population The clinical data of 159 primary ALL children treated in the department of Pediatrics, Sun Yat-Sen Memorial Hospital, from June 2008 to May 2012, were retrospectively analyzed, with the exclusion of those who were confirmed the hyperglycemia before the

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chemotherapy or with the family history of diabetes, as well as those who did not finish the inductive remission chemotherapy. All the patients were treated with the program of Guangzhou Child ALL 2008 chemotherapy collaboration committee, namely the VDLD program: vincristine (1.5 mg/m²/d) + daunorubicin (30mg/m²/d) + L-asparaginase (5000 IU/m²/d, q3d, with a total of 8 days) + steroid (prednisone 60 mg/m²/d, d1-7, oral administration; dexamethasone 6 mg/m²/d, d8-28, stopped gradually after the oral administration). the follow-up was performed till January 2014, with the median follow-up time as 3.2 years (0.08 to 5.6 years).

Data Collection:

Clinical data recording: age of the initial diagnosis, gender, risk stratification, blood glucose values during the inductive therapy, insulin treatment, diagnosis date, complete remission time, recurrence time, death or last follow-up date .

Definition of chemotherapy-related hyperglycemia: during the L-asparaginase and dexamethasone-contained inductive chemotherapy, the appearance of fasting plasma glucose ≥ 126 mg/dl and (or) random blood glucose ≥ 200 mg/dl was twice or more. every child was performed the blood glucose test more than twice. And the children were divided into the hyperglycemia group and the euglycemia group according to the blood glucose values.

Insulin treatment: the situation of random blood glucose ≥ 200 mg/dl would be performed the intensive insulin therapy (short-acting RI + middle-acting insulin NPH), while the situation of $126 \text{ mg/dl} \leq$ random blood glucose ≤ 200 mg/dl used the intensive insulin or pure short-acting insulin therapy or diet control, the treatment program was individualized, the blood sugar control target: the random blood glucose $< 110 \sim 126$ mg/dl (7~8 mmol/l).

Risk stratification: According to the program of Guangzhou Child ALL 2008 chemotherapy collaboration committee, the risks were divided into the standard risk (SR), interim risk (IR) and high risk (HR), SR: met all of the following points: the 7d response of prednisone was good, the 8th-d peripheral blood juvenile cells $< 1.0 \times 10^9/L$; age ≥ 1 year old and < 6 years old ; WBC $< 20 \times 10^9/L$; the marrow M1 on the 15th inductive chemotherapy day (primary lymphocytes + immature lymphocytes $< 5\%$) or M2 (primary lymphocytes + immature lymphocytes 5% to 25%) ; the marrow M1 on the 33rd inductive chemotherapy day. IR: met all the following points: prednisone response was good, the 8th-d peripheral blood juvenile cells $< 1.0 \times 10^9/L$; age < 1 year old or ≥ 6 years old ; WBC $\geq 20 \times 10^9/L$; the marrow M1 or M2 on the 15th inductive chemotherapy day; the marrow M1 on the 33rd inductive chemotherapy day, or complies with the SR standard, while the marrow M3 on the 15th inductive chemotherapy day (primary lymphocytes + immature lymphocytes $> 25\%$), the marrow M1 on the 33rd inductive chemotherapy day . HR: met at least one of the following: non- SR and marrow M3 on the 15th inductive chemotherapy day; prednisone response was poor, the 8th-d peripheral blood juvenile cells $\geq 1.0 \times 10^9/L$; the marrow M2 or M3 on the 33rd inductive chemotherapy

day; existed the abnormality of t (9:22) (BCR/ABL) or t (4; 11) (MLL/AF4).

Definition of prognostic index: the recurrence of ALL includes the marrow recurrence and central nervous system relapse. CR was defined as the bone marrow initial cells $< 5\%$, and the bone marrow restore the normal hematopoietic function. RFS was defined as the date from the diagnosis to the relapse, death or final follow-up. OS was defined as the date from the diagnosis to the death or final follow-up.

Statistical Analyses: All the data were statistically analyzed using SPSS17.0 software . the 5-year overall survival rate and relapse-free rate used the Kaplan-Meier method, and were performed the log-rank test to compare the difference of survival curves between the hyperglycemia group and the non- hyperglycemia group ; the risk factor analysis of hyperglycemia used the X² test, the CR rate comparison of the 2 groups used the Fisher exact test; the non-normally distributed measurement data were expressed by the median, while the counting data used the X² test, with $P < 0.05$ considered as the statistical significance.

Results

High-risk factor analysis of chemotherapy-related hyperglycemia

The median age of the patients in this research when initially diagnosed was 4.7 years old (1.1 to 16.8 years old). Among the 159 children, 38 patients (23.90%) occurred the chemotherapy-related hyperglycemia, and divided into the hyperglycemia group, among who the glucose level of 10 (6.29%) was ≥ 200 mg/dl, while without the case of ketoacidosis; 121 patients (76.1%) did not appear the hyperglycemia, thus divided in the euglycemia group. Within the 38 cases of the hyperglycemia group, 16 cases (42%) were performed the insulin treatment. The hyperglycemia rate of the high-age group (≥ 10 years old) was higher than that of the lower-age group (43.33% VS 19.38%), and the difference was statistically significant ($P = 0.009$), and the incidences of the interim- and high-risk groups were higher than the standard risk group (26.81% VS 4.76%, $P = 0.028$), while relevant to the gender ($P = 0.056$).

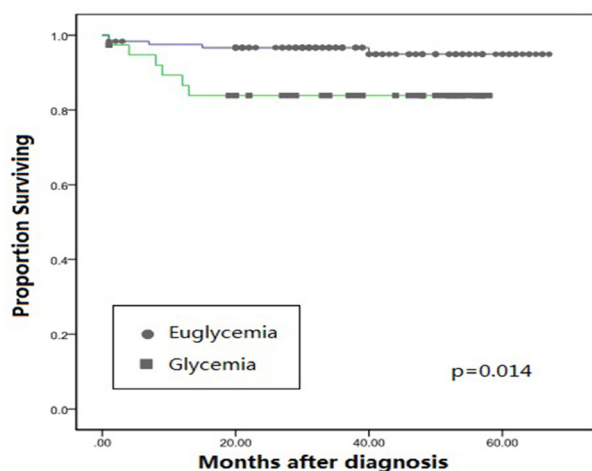
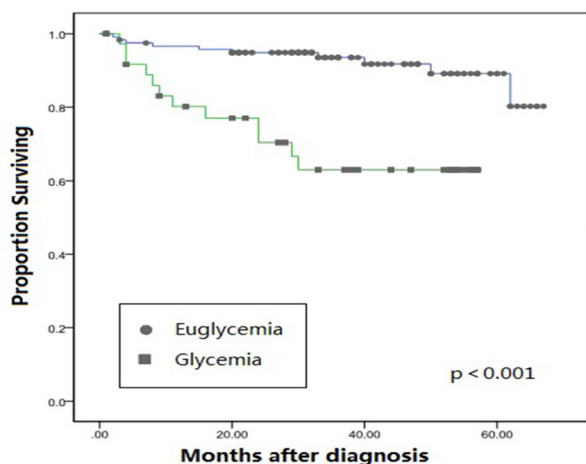
CR conditions of the 2 groups at the end of inductive

Table 1. Risk Factors and Remission Conditions of Hyperglycemia During the Inductive Chemotherapy

	Hyperglycemia	Euglycemia	P value
Percentage (%)	23.9	76.1	
Median age (yr) at diagnosis			0.009
$\geq 10(30)$	13 (43.3%)	17 (56.7%)	
$> 10(129)$	25 (19.4%)	104 (80.6%)	
Sex			0.056
Male (117)	23 (19.7%)	94(80.3%)	
Female (42)	15 (35.7%)	27(64.3%)	
Risk assignment			0.028
Low (21)	1 (4.76%)	20 (95.2%)	
Standard/High (138)	37 (26.8%)	101 (73.2%)	
CR rate			0.134
CR	33 (86.8%)	115 (95.0%)	
NR	5 (13.2%)	6 (5.00%)	

Table 2. Survival Analysis of Hyperglycemia Group and Euglycemia Group

Variables	Events	OS	SE	P value	Event	RFS	SE	P value
Hyperglycemia	6	83.8%	6.0%	0.014	12	62.9%	8.7%	<0.001
Euglycemia	5	94.9%	2.4%		10	80.2%	9.1%	

**Figure 1. KM Survival Curves of 5-Year Overall Survival Rate of the 2 Groups (Log-Rank Test)****Figure 2. KM Survival Curves of 5-Year Relapse-Free Rate of the 2 Groups (Log-Rank Test)**

chemotherapy: among the 38 cases of the hyperglycemia group, 33 cases achieved CR (86.8%), while among the 121 cases of the euglycemia group, 115 cases achieved CR (95%), there was no significant difference between the two groups ($P=0.134$)

The analysis of risk factors and remission conditions of hyperglycemia during the inductive chemotherapy was shown in Table 1.

Survival analysis

The follow-up was performed until Jan 2014, and among the 159 included inside the statistics, 21 cases relapsed (with relapse rate as 13.21%), 11 cases died (including 4 cases of deaths with the relapse); among the 38 cases of the hyperglycemia group, 11 cases relapses (with the relapse rate as 28.95%), 6 cases died (including 2 cases of deaths with the relapse).

The Kaplan-Meier method was used to compare the accumulative 5-year survival rates and the relapse-free

rates of the two groups, and the results were shown in Table 2 and Figures 1 and 2. The accumulative 5-year overall survival rate of the hyperglycemia group was $83.8\pm 6.0\%$, significantly lower than that of the euglycemia group ($94.9\pm 2.4\%$), $P=0.014$; Similarly, the accumulative 5-year relapse-free rate of the hyperglycemia group was ($62.9\pm 8.7\%$), significantly lower than the euglycemia group ($80.2\pm 9.1\%$), $P<0.001$.

These results suggested that the prognosis of the hyperglycemia group was poorer, with its recurrence rate and mortality rate higher than the non-chemotherapy-related hyperglycemic children.

Discussion

The current cure rate of child ALL has been improved significantly, but there is still 25%~30% of relapse, and the post-relapse treatment is still the bottleneck towards the improvement of the overall prognosis of child ALL, and the clearance of high risk factor that would lead to the relapse of child ALL might reduce the recurrence. The clinical data of adult ALL indicated that the occurrence of hyperglycemia during the inductive remission period was the independent risk factor that affected the ALL relapse and high mortality rate (Weiser et al., 2004). The impacts of hyperglycemia occurrence during the inductive remission period towards the prognosis of child ALL is still not clear. The results of this research suggested that the hyperglycemia occurrence during the inductive remission period was connected with the poor prognosis of child ALL, the accumulative 5-year relapse-free survival rate and the overall survival rate of the hyperglycemia group were significantly lower than the euglycemia group.

In this study, a total of 159 children were included into the statistics, and the hyperglycemia occurrence rate during the inductive chemotherapy was 23.9%, the proportion of blood glucose level ≥ 200 mg/dl for twice or more was 6.29% (10/159), similar to the previous researches (4% to 20%), while significantly lower than the report of Rona (58%), in which the proportion of blood glucose level ≥ 200 mg/dl for twice or more was as high as 34%, and that might be related with the higher proportion of obese children and the high proportion of postprandial glucose detection (Sonabend et al., 2009). The combination of L-asparaginase and glucocorticoids, as well as the disease stress, might be the main reason of hyperglycemia (Vu et al., 2012), whether the types of glucocorticoids (prednisone or dexamethasone) would affect the hyperglycemia incidence is still controversial, and the leukemia itself might also affect the glucose metabolism, appearing as the elevated level of basic glycosylated hemoglobin, insulin resistance or insulin receptor abnormalities (Roberson et al., 2008; Sonabend et al., 2009; Spinola-Castro et al., 2009).

In this study, the newly-onset ALL children had the median age as 4.6 years old, and the hyperglycemia incidence among the age ≥ 10 -year-old children was significantly higher than the lower age group (43.33% VS 19.23%, $P=0.008$), and the incidences of the interim and high-risk groups were significantly higher than the standard-risk group (22.53% VS 5.33%, $P=0.017$). 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, the incidence of the hyperglycemia group was higher (Roberson et al., 2008; Lowas et al., 2009; Roberson et al., 2009; Sonabend et al., 2009; Spinola-Castro et al., 2009), and thus became the index of poor prognosis in a number of collaborative groups.

In this study, the occurrence of hyperglycemia during the inductive chemotherapy did not significantly affect the CR rate of children (compared with the euglycemia group, 86.8% vs 95%, $P=0.134$), while the prognosis of the hyperglycemia group was poorer, the 5-year overall survival rate was significantly lower than the euglycemia group ($83.1\pm 6.3\%$ vs $94.2\pm 2.9\%$, $P=0.014$), the 5-year relapse-free rate was also significantly lower than the euglycemia group ($64.1\pm 8.9\%$ vs $88.6\pm 3.8\%$, $P<0.001$). Several studies of adults had shown that the hyperglycemia could predict the higher mortality, the mean fasting blood glucose >112.5 mg/dl could significantly increase the mortality of cancer patients (Bochicchio et al., 2010; Seshasai et al., 2011), and the appearance of hyperglycemia in the inductive chemotherapy of adult ALL patients exhibited the poor prognosis, compared with the euglycemic patients, the risks of the early recurrence and higher mortality were 1.57 times and 1.71 times, respectively, with shorter median CR (24 months vs 52 months, $P=0.001$) and median survival time (29 months vs 88 months, $P<0.001$) (Weiser et al., 2004). currently, there were three research institutions that reported the relationship of hyperglycemia during the inductive remission with the childhood ALL, while the results were different. the results of Sonabend were similar to our conclusions, when the blood glucose of ALL children was greater than 200 mg/dl, compared with other ALL children, the 5-year recurrence rate ($68\%\pm 6.7\%$ vs $85\%\pm 3.6\%$, $P=0.025$) and the overall survival ($74\%\pm 6.1\%$ vs $96\%\pm 1.9\%$, $P<0.0001$) were significantly reduced, while the risk of death was 6.2 times than that of other ALL children, thus the blood glucose level ≥ 200 mg/dl was an independent predictor of survival towards the ALL children (Sonabend et al., 2009). while the study of Roberson did not draw the conclusions about the relationship of hyperglycemia during the inductive chemotherapy and poor prognosis of the ALL children, the overall survival rates and the accumulative recurrence rate between the two groups did not exist the significant differences (Roberson et al., 2009), the sample size of Spinola was too small (12 patients, with 16 times of hyperglycemia detected), although it was unable to confirm the relation of hyperglycemia and poor prognosis of the ALL children, the author believed that it would be of great importance to evaluate the changes of blood glucose level during the ALL inductive chemotherapy period (Spinola-Castro et al., 2009). the reason that the conclusions of Sonabend and Roberson existed the difference was still unclear, which might because of the different constitution of research subjects (age, risk degree, immune status, infection and delay effects of chemotherapy), different degrees of hyperglycemia (incidence rate as 34% vs 16%), different remedial methods after the relapse (whether performed

the stem cell transplantation) and others.

The conventional view was that the hyperglycemia could mainly reduce the patients' immunity, increase the chances of infection (the blood glucose of the hyperglycemia group was 2.1 to 2.5 times than the euglycemia group), delay the chemotherapy, decrease the clearance of leukemic minimal residual lesions, thus affecting the effects of ALL treatment (Weiser et al., 2004; Sonabend et al., 2008). Now, it's considered that the relationships between the abnormal glucose metabolism and the poor prognosis of cancer are multifactorial, the cancer cells could downregulate P53 to affect the stability of glucose metabolism, while the hyperglycemia could provide more energy towards the tumor cell growth by the glycolytic pathway (Yeung et al., 2008), in the type 2 diabetes patients who exist the insulin resistance, the hyperinsulinemia and high insulin-like growth factor (IGF) levels would downregulate P53 by the AKT signaling pathway. The insulin exists the somatomedin-like properties, the recent experiments have found that the high-level insulin and glucose concentration could promote the growth of a variety of tumor cells (pancreatic cancer, breast cancer, hepatocellular carcinoma, ALL primary cells and cell lines) via both independent and synergic mechanisms, while the insulin might reduce the tumor cell apoptosis and induce their drug resistance (Brown et al., 2008; Feng et al., 2011; Pan et al., 2012).

Currently, the inductive chemotherapy-induced hyperglycemia is still using the insulin to control the blood sugar clinically. The research of critically ill patients in 2009 found that: the mortality rate of the patients with the control objective of blood glucose level as 81~108 mg/dl (intensive insulin therapy) was significantly higher than the patients with the blood glucose controlled in 180 mg/dl (conventional insulin therapy) or in a slightly lower level (OR 1.14, 95%CI 1.02-1.28, $P=0.02$). the prospective clinical study of adult ALL and lymphoma also found that during the intensive insulin therapy towards the poor prognosis of hyperglycemia, the level of insulin/C-peptide >0.175 indicated the decreased overall survival rate ($P=.0016$) and relapse-free survival rate ($P=0.0002$), as well as CR was shortened ($P=.0042$) (Vu et al., 2012). there had not been reported about the characteristics of glucose metabolism in the inductive remission period of child ALL, and the impacts and dosage-efficacy relationships of insulin therapy towards the child ALL prognosis are not clear, thus it could not rule out that the different intensities of insulin therapy might exhibit certain impacts towards the research findings. Sonabend mentioned only 56 cases of hyperglycemia (glucose level ≥ 200 mg/dl), among who 16 cases were treated with the insulin (28.6%), while Roberson stressed that the insulin therapy was just for a short period, once the glucose level was <200 mg/dl and did not rise again (including the patients of ketoacidosis), the insulin therapy should be stopped, but the usage of insulin had no fixed guidelines, the both reports of Sonabend and Roberson did not provide the detailed intensity of insulin therapy. In this study, among the 38 hyperglycemic patients, 16 cases were treated with the insulin, the proportion of insulin therapy was higher (42%), and the blood sugar control target as <

110~126 mg/dl also indicated that the intensity of insulin therapy was higher, which also might be associated with the poor prognosis of the hyperglycemic children .

The limits of this study lied in the use of a retrospective analysis, thus the impacts of insulin therapy intensity towards the prognosis of hyperglycemic ALL children could not be assessed; and the differences of hyperglycemia towards the severe infection rate and delays of chemotherapy in the euglycemic children were not evaluated ; and the sample size of hyperglycemic children was small (38 cases).

The results of this study showed that the prognosis of the ALL children, who occurred the hyperglycemia during the inductive chemotherapy, was poorer than those with euglycemia, and the accumulative 5-year survival and relapse-free rate were significantly reduced. Therefore, in the clinical works, the monitoring towards the blood glucose level should be paid attention to during the inductive chemotherapy, especially towards the population with high-risk of hyperglycemia, it should be active to prevent the occurrence of hyperglycemia . The proportion of insulin used in this study (42%) and the greater usage intensity could not be excluded from the association with the poor prognosis, which needed the prospective and randomized controlled study for the further confirmation. The effective prevention and treatment of hyperglycemia would help to improve the overall prognosis of ALL children.

Acknowledgements

This study was supported by National Nature Scientific Grant of China (No. 30772367) and Nature Scientific Grant of Guangdong Province (No. S2011010002648) and International Cooperation Grant of Guangdong Province (No. 2011B050400023).

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