Post-Print of a Clinical Study on Hyperglycemia Secondary to Modified Hyper-CVAD Induction Therapy in Middle-aged and Elderly Patients with Ph-Negative Acute Lymphoblastic Leukemia

Authors: Ye Huicheng (1); Liu Yuhua (2)

Date: 2017-12-07T00:00:00+00:00

Abstract

Objective To investigate the impact of the modified Hyper-CVAD regimen on blood glucose in middle-aged and elderly patients with Ph-negative acute lymphoblastic leukemia, and to explore the relationship between blood glucose and prognosis.

Methods Seventy-two middle-aged and elderly patients with Ph-negative acute lymphoblastic leukemia were randomly selected and divided into Group A and Group B, with 36 patients in each group. Group A received modified Hyper-CVAD induction chemotherapy, while Group B received conventional Hyper-CVAD regimen treatment. Clinical characteristics, incidence of secondary hyperglycemia, and post-chemotherapy survival status were compared between the two groups before and after chemotherapy, and patients were followed up for 3 years.

Results At the end of week 3, random blood glucose in the control group was higher than that in the observation group (8.03±2.73 mmol/L vs 7.85±2.54 mmol/L), and higher than the control group' s own random blood glucose at the end of week 1 (8.03±2.73 mmol/L vs 7.37±2.19 mmol/L, $P<0.05$). At the end of week 4, both fasting and random blood glucose in both groups were higher than their own values at the end of week 1, and random blood glucose in the control group was significantly higher than that in the observation group (8.57±3.32 mmol/L vs 8.03±2.59 mmol/L, $P<0.05$), but there was no statistically significant difference in fasting blood glucose between the two groups ($P>0.05$). The incidence of secondary hyperglycemia in the control group was 22.22%, significantly higher than 5.56% in the observation group ($P<0.05$), but there was no statistically significant difference in relapse rate or survival rate

between the two groups. Both fasting and random blood glucose at the end of week 4 in both groups were correlated with infection, remission rate, relapse rate, and overall survival rate. Relapse occurred in 11 and 14 cases respectively in the two groups, but the difference in relapse rate was not statistically significant (30.56% vs 38.89%, P=0.458); 9 and 12 patients died respectively in the two groups, and the difference in survival rate was not statistically significant (75.00% vs67.67%, P=0.437).

Conclusion The modified Hyper-CVAD regimen can effectively reduce the incidence of secondary hyperglycemia in middle-aged and elderly patients with Ph-negative acute lymphoblastic leukemia.

Full Text

Clinical Study of Modified Hyper-CVAD Induction Therapy for Secondary Hyperglycemia in Elderly Patients with Ph-Negative Acute Lymphoblastic Leukemia

Ye Huicheng[1], Liu Yuhua[2] [1]Department of Endocrinology; [2]Department of Integrated Medicine, Dongguan People' s Hospital, Dongguan, Guangdong 523059, China

Abstract

Objective: To investigate the effect of a modified Hyper-CVAD regimen on blood glucose levels in elderly patients with Ph-negative acute lymphoblastic leukemia (ALL) and to explore the relationship between hyperglycemia and prognosis.

Methods: Seventy-two elderly patients with Ph-negative ALL were randomly selected and divided into two groups (A and B) of 36 patients each. Group A received modified Hyper-CVAD induction chemotherapy, while Group B received conventional Hyper-CVAD therapy. Clinical characteristics, secondary hyperglycemia incidence, and post-chemotherapy survival status were compared between the two groups before and after treatment. Patients were followed up for three years.

Results: The control group showed higher random blood glucose at week 3 compared to the observation group (8.03±2.73 mmol/L vs 7.85±2.54 mmol/L) and also higher than its own week 1 values (8.03±2.73 mmol/L vs 7.37±2.19 mmol/L, P<0.05). By week 4, both groups exhibited elevated fasting and random blood glucose compared to baseline, with the control group' s random glucose significantly higher than the observation group' s (8.57±3.32 mmol/L vs 8.03±2.59 mmol/L, P<0.05), though fasting glucose differences were not statistically significant (P>0.05). The incidence of secondary hyperglycemia was 22.22% in the control group versus 5.56% in the observation group (P<0.05), while no significant differences were observed in recurrence or survival rates. Both fasting and

random blood glucose at week 4 correlated with infection rates, remission rates, recurrence rates, and overall survival. Recurrence occurred in 11 and 14 cases respectively (30.56% vs 38.89%, P=0.458), and 9 versus 12 deaths were recorded (75.00% vs 67.67%, P=0.437), with no statistically significant differences.

Conclusion: The modified Hyper-CVAD regimen effectively reduces the incidence of secondary hyperglycemia in elderly patients with Ph-negative acute lymphoblastic leukemia.

Keywords: modified Hyper-CVAD; elderly patients; Ph-negative; acute lymphoblastic leukemia; hyperglycemia

Introduction

Research on chemotherapy-induced hyperglycemia in childhood acute lymphoblastic leukemia (ALL) is well-established, whereas studies in adult ALL, particularly among elderly patients, remain relatively scarce. The Hyper-CVAD regimen has emerged as an international standard for ALL treatment, demonstrating favorable efficacy but also significant adverse effects, with secondary hyperglycemia being particularly common. Abnormal glucose metabolism may affect tumor cell metabolism and clinical outcomes, prompting the development of modified Hyper-CVAD protocols with reduced endocrine and metabolic impact. However, reports on Hyper-CVAD-induced glucose abnormalities in elderly ALL patients remain limited. To investigate the effects of modified Hyper-CVAD on blood glucose in elderly Ph-negative ALL patients and explore the relationship between glucose levels and prognosis, we conducted a study of 72 patients, finding that the modified regimen effectively reduces the incidence of secondary hyperglycemia.

Methods

Patient Selection

We enrolled 72 newly diagnosed elderly Ph-negative ALL patients who received modified Hyper-CVAD induction therapy in our endocrinology department between January 2010 and December 2016. Inclusion criteria were: (1) diagnosis according to WHO 2008 classification standards for lymphoid and hematopoietic tumors; (2) age 55 years; (3) adequate organ function (total bilirubin 2×upper normal limit; ALT and AST 2.5×upper normal limit; creatinine clearance 50 mL/min); and (4) ECOG performance status 3. Exclusion criteria included: (1) prior impaired glucose tolerance or diabetes history; (2) glucocorticoid use within one month before chemotherapy; (3) Ph-positive ALL; and (4) poor compliance or refusal of chemotherapy. Patients were randomly divided into observation and control groups (n=36 each) receiving different treatment protocols. The observation group (modified Hyper-CVAD) included 21 males and 15 females aged 51-71 years, while the control group (conventional Hyper-CVAD) comprised 23 males and 13 females aged 50-70 years. No statistically significant

differences existed between groups in gender distribution, age, disease course, white blood cell count, bone marrow immunophenotyping, chromosomal abnormalities, or BCR gene fusion rate (P>0.05,). Baseline fasting glucose, random glucose, and glycated hemoglobin levels were also comparable between groups (P>0.05,).

Treatment Protocols

Modified Hyper-CVAD (Observation Group): The regimen alternated between A and B cycles every 28 days. Cycles 1, 3, 5, and 7 used the A 方案: cyclophosphamide (CTX) 300 mg/m² every 12 hours on days 1-3; dexamethasone (DEX) 40 mg/d on days 1-4 and 11-14; vindesine 2-4 mg on days 4 and 11; and pirarubicin (THP) 50 mg/m² on day 4. Cycles 2, 4, 6, and 8 employed the B 方案: methotrexate (MTX) 1 g/m² on day 1; cytarabine (Ara-C) 1-2 g/m² on days 2-3 (reduced to 0.5 g/m² every 12 hours for patients >60 years).

Conventional Hyper-CVAD (Control Group): The A 方案 consisted of CTX 300 mg/m² twice daily on days 1-3 with mesna 600 mg/(m² · d) administered in three divided doses at start of CTX infusion and at 4 and 8 hours; vincristine (VCR) 2 mg on days 4 and 11; pirarubicin 50 mg/m² on day 4; and dexamethasone 40 mg/d orally or intravenously on days 1-4 and 11-14. After hematopoietic recovery, the B 方案 was administered: MTX 2 g/m² intravenously over 2 hours, increased to 0.8 g/m² over 22 hours on day 1; Ara-C 1.0-1.5 g/m² twice daily on days 2-3. Leucovorin 50 mg/m² was given intravenously every 6 hours for 8 doses starting 12 hours after MTX to reduce toxicity.

Both groups received prophylactic intrathecal MTX and/or Ara-C with dexamethasone each cycle to prevent central nervous system leukemia. After eight cycles, patients entered maintenance therapy: prednisone 1 $mg \cdot kg^{-1} \cdot d^{-1}$ on days 1-7 monthly; vindesine 2-4 mg on day 1; oral MTX 20 mg/m² weekly; and oral 6-mercaptopurine 60 $mg \cdot m^{-2} \cdot d^{-1}$ on days 1-21, continuing for two years post-remission.

Data Collection and Definitions

General data included age, gender, BMI, time to diagnosis, initial blood cell counts, bone marrow immunophenotyping, karyotype, BCR/ABL fusion gene status, infection during induction, early mortality, recurrence, and overall survival. Blood glucose indicators comprised fasting and random glucose levels and HbA1c at diagnosis, plus dynamic glucose monitoring during one month of induction therapy. Chemotherapy-related hyperglycemia was defined as: during induction, 2 consecutive fasting glucose measurements 126 mg/dL (7.0 mmol/L) and/or 2 consecutive random glucose measurements 200 mg/dL (11.1 mmol/L).

Statistical Analysis

SPSS 17.0 software was used for statistical analysis. Categorical data were expressed as percentages and compared using ^{2} tests. Continuous data were presented as mean±standard deviation and compared using t-tests. P<0.05 was considered statistically significant.

Results

Blood Glucose Levels

No significant differences in fasting or random glucose were observed between groups at weeks 1 and 2. At week 3, the control group' s random glucose was higher than the observation group' s (P<0.05) and exceeded its own week 1 values (P<0.05), though fasting glucose remained comparable. By week 4, both groups showed elevated fasting and random glucose compared to baseline (P<0.05). The control group' s random glucose was significantly higher than the observation group' s (8.57±3.32 mmol/L vs 8.03±2.59 mmol/L, P<0.05), but fasting glucose differences were not statistically significant ().

Hyperglycemia, Recurrence, and Survival

Secondary hyperglycemia occurred in 8 control group patients (22.22%) versus only 2 in the observation group (5.56%), a statistically significant difference (P<0.05). Recurrence was observed in 11 (30.56%) and 14 (38.89%) patients respectively, without significant difference (P=0.458). Nine versus twelve deaths occurred, yielding survival rates of 75.00% and 67.67% respectively (P=0.437), also without statistical significance ().

Correlation Analysis

Both fasting and random glucose at week 4 correlated with infection rates, remission rates, recurrence rates, and overall survival (P<0.05). The strongest correlation was between random glucose and overall survival (r=0.845, P=0.003), followed by correlation with remission rate (r=0.822, P=0.011) ().

Discussion

Acute lymphoblastic leukemia exhibits strong heterogeneity across age groups. While advances in allogeneic hematopoietic stem cell transplantation and tyrosine kinase inhibitor therapy have improved outcomes for childhood ALL, treatment progress for elderly patients has been slow, remaining a major clinical challenge. Moreover, adult Ph-negative ALL lacks indications for molecular targeted therapies like imatinib, making treatment particularly difficult. The relatively low remission rates and poor survival status in elderly ALL patients are significantly associated with treatment modalities. Elderly patients have multiple comorbidities and declining organ function, making them less tolerant

to intensive chemotherapy, while low-dose combination chemotherapy fails to effectively suppress leukemic cell clones. Chemotherapy also frequently causes severe adverse reactions, particularly hyperglycemia (incidence 4-20%), which can lead to additional metabolic abnormalities such as lipid metabolism disorders and substantially reduce clinical efficacy. Previous studies have established that hyperglycemia in adult ALL correlates with early relapse and high mortality, with even worse prognosis when hyperglycemia occurs in elderly patients. Research has also shown that different combination regimens and dosages yield varying incidences of secondary diabetes.

Since 1992, the MD Anderson Cancer Center has used Hyper-CVAD for ALL treatment, designed based on cyclophosphamide' s 6-hour half-life with fractionated high-dose administration to maintain therapeutic concentrations for 72 hours, maximizing coverage of tumor cell proliferation cycles while avoiding drug resistance. Although effective, Hyper-CVAD causes severe complications that particularly impact elderly patients with poorer physiological reserves. Therefore, we modified the regimen to improve its applicability for elderly ALL patients.

Our findings show that both modified and conventional Hyper-CVAD groups developed hyperglycemia, confirming that chemotherapy can induce hyperglycemia in ALL patients, consistent with Dare et al. Previous adult ALL studies often adopted pediatric protocols, neglecting age-related differences and yielding insufficiently representative results. Our study used an adult-specific Hyper-CVAD regimen, allowing investigation of age-related prognostic effects while comparing treatment approaches, producing more compelling results.

Notably, the conventional Hyper-CVAD group showed significantly higher secondary hyperglycemia rates (22.22% vs 5.56%) and higher infection rates than the modified regimen group, suggesting that modifications effectively reduce hyperglycemia and associated infection risk. Studies using conventional Hyper-CVAD have reported frequent myelosuppression and severe bacterial infections. Our modifications, based on Chinese patients' characteristics and clinical experience, adjusted drug types and dosages, resulting primarily in gastrointestinal reactions and mild non-hematological toxicities such as hepatic injury, demonstrating improved tolerability and safety that facilitates investigation of treatment-related diabetes.

Unlike Pan et al.' s pediatric study showing older children had higher hyperglycemia risk, our elderly-focused research demonstrates that elderly ALL patients are prone to secondary hyperglycemia, with elevated glucose levels correlating positively with infection, remission, recurrence, and overall survival rates, indicating that hyperglycemia significantly impacts survival. Although our groups' complete remission rates were lower than MD Anderson' s 91%, long-term follow-up showed favorable disease-free survival and clinical efficacy. However, despite different hyperglycemia rates, recurrence and survival rates did not differ significantly between groups, contrasting with Liu et al.' s findings that modified Hyper-CVAD prolongs survival and reduces recurrence. This

discrepancy may relate to our smaller sample size and shorter follow-up duration, requiring further investigation to fully evaluate our modified regimen' s value.

In summary, the modified Hyper-CVAD induction regimen reduces the risk of secondary hyperglycemia in elderly Ph-negative ALL patients with good therapeutic efficacy, warranting clinical promotion. Whether the modified regimen offers greater advantages in prolonging disease-free survival requires further evidence-based research.

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Note: Figure translations are in progress. See original paper for figures.