Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2012 October ; 12(5): 355–362. doi:10.1016/j.clml.2012.05.004.

A randomized controlled trial of an intensive insulin regimen in hyperglycemic acute lymphoblastic leukemia patients

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Abstract

INTRODUCTION—Hyperglycemia during hyper-CVAD chemotherapy is associated with poor outcomes of acute lymphoblastic leukemia (ALL).

PATIENTS/METHODS—To examine whether an intensive insulin regimen could improve outcomes compared with conventional anti-diabetic pharmacotherapy, a randomized trial was conducted comparing glargine plus aspart versus conventional therapy (control). Between 4/2004 and 7/2008, 52 newly diagnosed ALL, Burkitt's lymphoma, or lymphoblastic lymphoma patients on hyper-CVAD in the inpatient setting and had random serum glucose >180 mg/dL in 2 occasions during chemotherapy were enrolled.

RESULTS—The trial was terminated early due to futility regarding ALL clinical outcomes despite improved glycemic control. Secondary analysis revealed that molar insulin-to-C-peptide ratio (I/C) >0.175 (a surrogate measure of exogenous insulin usage) was associated with decreased overall survival, complete remission duration and progression-free survival (PFS) while metformin and/or thiazolidinedione usage were associated with increased PFS. In multivariate analyses, factors which significantly predicted short overall survival included age ≥60 years

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Trial registration: <http://www.ClinicalTrials.gov> NCT00500240

FINANCIAL DISCLOSURE & CONFLICTS OF INTERESTS

Dr. Vu has grant support from Novo-Nordisk. Dr. Busaidy has grant support from Bayer. All other authors have no conflicts of interests to disclose. Financial support for the study was stated above in Acknowledgement. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

($P=0.0002$), I/C 0.175 ($P=0.0016$) and average glucose 180 mg/dL ($P=0.0236$). Factors that significantly predicted short progression-free survival included age ≥ 60 years ($P=0.0008$), I/C 0.175 ($P=0.0002$), high systemic risk ($P=0.0173$) and average glucose ≥ 180 mg/dL ($P=0.0249$). I/C 0.175 was the only significant ($P=0.0042$) factor that predicted short complete remission duration.

CONCLUSION—A glargine-plus-aspart intensive insulin regimen did not improve ALL outcomes in hyperglycemic patients. Exogenous insulin may be associated with poor outcomes while metformin and thiazolidinediones may be associated with improved outcomes. These results suggest that the choice of anti-diabetic pharmacotherapy may influence ALL outcomes.

Keywords

Diabetes; intensive insulin regimen; secretagogues; metformin; thiazolidinediones

INTRODUCTION

Epidemiologic data suggest important roles of type 2 diabetes mellitus (DM2) in carcinogenesis [1–4] and prognosis [5]. The hyper-CVAD regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and high-dose cytarabine with methylprednisolone premedication) is currently a standard treatment for acute lymphocytic leukemia (ALL), Burkitt's lymphoma (BL), and lymphoblastic lymphoma (LL) [6]. This regimen, which includes high-dose dexamethasone and methylprednisolone, frequently leads to hyperglycemia. Our retrospective study of 278 adult patients with previously untreated ALL who achieved a complete response with hyper-CVAD showed that hyperglycemia (glucose ≥ 200 mg/dL on ≥ 2 determinations) occurred in up to 37% of patients during induction chemotherapy [7]. Hyperglycemic patients had shorter median complete remission duration (CRD) (24 vs. 52 months, $P=0.001$) and a shorter median survival (29 vs. 88 months, $P<0.001$) than non-hyperglycemic (glucose <200 mg/dL on <2 determinations) patients [7]. When controlled for predictors of ALL outcomes in multivariate analysis, hyperglycemia was an independent factor for early relapse and mortality; patients with hyperglycemia were 1.57 times more likely to relapse and 1.71 times more likely to die than those without hyperglycemia [7].

Hyperglycemia is an independent predictor of in-hospital mortality, duration of hospitalization, and admission to an intensive care unit, among hospitalized patients with undiagnosed diabetes [8]. Improved glycemic control decreases the incidence of microvascular and probably macrovascular complications in patients with type 1 and type 2 diabetes mellitus [9–13]. Tight glucose control with intensive insulin therapy may reduce morbidity and mortality among critically ill patients [14]. Whether tight glucose control can improve outcomes in patients with malignancies has not been studied.

We conducted a prospective randomized trial to examine whether improving glycemic control using intensive insulin therapy could improve the clinical outcomes of ALL compared with conventional diabetes therapy in hyperglycemic ALL patients undergoing hyper-CVAD [15]. Here we report the full analysis of this clinical data. This study showed that an intensive insulin regimen with glargine and aspart was not able to improve the clinical outcomes of hyperglycemic ALL patients despite improved glycemic control. Secondary analysis suggested that exogenous insulin or analogues might worsen but metformin and/or thiazolidinediones might improve clinical outcomes of these patients.

PATIENTS & METHODS

This clinical trial was approved by Institutional Review Board of MD Anderson Cancer Center in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services. The study abided by the tenets of the recently revised Helsinki Protocol, including the provision for informed consent of participants.

Clinical Trial

A randomized prospective clinical trial was conducted under an approved protocol to determine whether tight glycemic control could result in improved clinical outcomes of hyperglycemic ALL, Burkits lymphoma (BL), or lymphoblastic lymphoma (LL) patients undergoing hyper-CVAD chemotherapy. Between 4/2004 and 7/2008, 52 newly diagnosed ALL, BL, or LL patients on hyper-CVAD in the inpatient setting and had random serum glucose >180 mg/dL in 2 occasions during chemotherapy were enrolled.

After informed consent, patients were randomized 1:1 to a conventional treatment arm or an intensive insulin intervention arm. Patients in the control arm were treated according to conventional care (glycemic control managed at the discretion of the attending physician). Regular glucose monitoring was not required. Their anti-diabetic medications potentially included insulin. Patients on the intervention arm received intensive insulin therapy with glargine and aspart in addition to dietary and educational interventions by diabetes educators and nutritionists. For patients with pre-existing DM2 randomized into this arm, all insulin secretagogues and insulin regimens were converted to glargine and aspart upon enrollment while other oral anti-diabetic agents were continued unless contraindicated. The initial glargine dose was estimated based on prior insulin dosage. On days that the patients received glucocorticoids, these patients used subcutaneous injections of glargine at prescribed doses and aspart based upon pre-prandial glucose according to a high-dose sliding scale. On days when they were not on glucocorticoids, they administered glargine at lower prescribed doses and aspart according to a low-dose sliding scale. The intensive insulin regimen was titrated individually to keep fasting blood glucose levels <120 mg/dL and postprandial glucose levels <180 mg/dL without hypoglycemia. Patients received intensive insulin therapy throughout consolidation chemotherapy.

Randomization Method

The randomization was done at The Clinical Oncology Research system (CORE), which is a clinical research information management system supporting clinical research trials at The University of Texas MD Anderson Cancer Center and collaborative sites across the nation. The randomization method used was balanced block randomization with blocks of 4 and 2 treatment regimens. After obtaining informed consent to participate in the study, the investigator, collaborator or research nurse will log on to the CORE website under this protocol to enroll the participant and receive the assignment of the participant to one of the two arms.

Clinical Laboratory Tests

Blood samples of all the patients were analyzed at the accredited clinical laboratory of The University of Texas MD Anderson Cancer Center. Measurements of insulin and c-peptide were sent out to be performed by a reference laboratory (Quest Diagnostics, Inc., Houston, TX).

Outcome Analyses

To evaluate the glycemic improvement in the intervention arm compared with the conventional treatment arm, the mean serum glucose level of all glucose measurements by

the clinical laboratory during each chemotherapy cycle for each patient was calculated and compared between the two groups. Since leukemic patients receive frequent transfusion of blood products, glycohemoglobin (hemoglobin A1c) was not a useful measure of glycemic control in these patients. The primary metric of clinical outcome is overall survival (OS) defined as the interval between the date of randomization and the date of death. Secondary metrics included the rates of complete remission (CR), complete remission duration (CRD), progression-free survival (PFS), infectious complications, hospitalizations, and ICU admissions. CR was defined as granulocyte count $>1.0 \times 10^9/L$, platelet count $>100 \times 10^9/L$, no abnormal peripheral blasts, and $<5\%$ blasts in normocellular or hypercellular bone marrow. CRD was defined as time from response to relapse or last follow-up. PFS was defined as the time interval between the date of complete remission and the date of relapse detection or death.

ALL patients who developed hyperglycemia on the hyper-CVAD had a median overall survival of 29 months [7]. Based on this expected median survival of the control arm, this trial was designed to test the hypothesis that intensive control of hyperglycemia would increase the median overall survival to 88 months (Type I error = 0.05). A total of 31 deaths would have been needed to detect this difference with 80% power. Therefore, we planned to enroll a total of 114 patients randomized equally between the two treatment arms. The interim monitoring was based on the Lan-DeMets alpha-spending function. The interim analysis was conducted after one half of the total number of expected deaths had been observed. The trial would have been stopped early for superiority if the z-value of the log-rank statistic comparing overall survival was > 2.96 or stopped for futility if the z-value of the log-rank statistic comparing overall survival was < 0.35 . If the trial had continued to the maximum sample size, a z-value > 1.95 would have been required to conclude superiority of intensive insulin regimen and in order to retain an overall Type I error rate of 0.05.

Patient characteristics and metrics of clinical outcome were tabulated and compared between treatment arms with the χ^2 -test or Wilcoxon's rank sum test as appropriate. OS, CRD and PFS were estimated according to the Kaplan-Meier method. Cox proportional hazards modeling was used to assess intensive insulin therapy and other patient characteristics in predicting outcomes. Factors in the model were chosen based on known prognostic factors for ALL [16], basic patient demographics, metabolic characteristics and drug treatments.

Trial registration

Registered at ClinicalTrials.gov: NCT00500240

RESULTS

Intensive insulin regimen did not improve the prognosis of ALL patients with hyperglycemia

Recruitment began on 4/27/2004 and follow up ended on 1/20/2010 (Figure 1). At interim analysis in 7/2008, patient enrollment was stopped by the Institutional Data Safety and Monitoring Board due to futility. There were 26 patients each enrolled in the conventional treatment arm and the intensive insulin intervention arm. One patient in the control arm was deemed unevaluable due to active management by an outside endocrinologist. There was a trend that the OS in the intensive insulin therapy arm was worse than the control arm, and if the trial had continued to maximum enrollment or the expected number of deaths, the probability of concluding in favor of the intensive insulin therapy arm was 0.0001 and the probability of concluding in favor of the conventional arm was 0.12.

Patient demographic and clinical characteristics of the 2 originally assigned arms are shown in Table 1. There were 51 evaluable patients with 23 deaths. The median OS was 62.2

months. One-year survival was 72.6% and 4-year survival was 52.9%. Treatment groups were balanced in terms of race, gender, and diagnosis. The median age of the patients in the intensive insulin arm was 11 years older than that of conventional treatment arm. When one patient in the conventional control arm was excluded due to active diabetes management by an outside endocrinologist, the age difference between the arms became significant ($P=0.047$). Thirteen of 25 patients in the conventional therapy received scheduled insulin or insulin analogues. The mean serum glucose levels in the intensive insulin arm were <180 mg/dL (Figure 2A). Mean glucose levels were significantly lower in the intensive insulin arm than the conventional therapy arm (repeated measures model with terms for treatment arms, cycles, and the interaction between the two, $P=0.019$). Within treatment arms, glucose levels were not different across chemotherapy cycles ($P=0.480$). There were no important harms or unintended effects in each group. The OS (Figure 2B) was not different between the two arms. Secondary outcome metrics are shown in Table 2. CR rate, proportion of patients with an ICU admission, number of hospitalizations, number of days of hospitalization, and number of infections were not different between the two arms. Of the 51 patients, there were 16 who relapsed and 35 who did not. The median CRD was not estimable. Of the 51 patients, there were 28 who relapsed and/or died, and the median PFS was 38.8 months. The CRD (Figure 2C) and PFS (Figure 2D) were not different between the two arms. Therefore, despite improved glycemic control, intensive insulin therapy did not improve the clinical outcomes of hyperglycemic ALL patients undergoing hyper-CVAD chemotherapy.

Factors associated with survival, complete remission duration and progression-free survival in hyperglycemic ALL patients

Pretreatment characteristics of ALL and the metabolic characteristics during hyper-CVAD chemotherapy were assessed for prognostic influence in exploratory analysis. Age, CD20 expression, leukocyte count, and systemic risk (high systemic risk includes presence of Philadelphia chromosome, leukocyte count $> 5 \times 10^9/L$, CNS disease, and > 1 course to CR) are prognostic factors for ALL while gender, CNS risk, percent peripheral blasts, percent marrow blasts, splenomegaly, hepatomegaly, and lymphadenopathy were not significant [16]. In our data set, age ≥ 60 years was a significant prognostic factor for OS ($P<0.0001$) and PFS ($P=0.0014$), but not for CRD ($P=0.57$). CD20 expression $\geq 20\%$, leukocyte count $> 30 \times 10^9/L$ and average serum glucose <180 mg/dL were not significant factors for OS, CRD and PFS in univariate analysis.

Proinsulin is cleaved into C-peptide and insulin and C-peptide is co-secreted on an equimolar basis. In the peripheral circulation, the molar ratio of insulin to C-peptide (I/C) is not 1 because of their different elimination half-lives. Nevertheless, supraphysiological fasting I/C implies exogenous insulin usage. Based on a study by Chen and Scholl [17], we used 2 standard deviations above the mean of the ethnic group with the highest I/C (i.e., 0.175) as a cutoff value above which significant exogenous insulin usage is implied. Insulin and C-peptide from the same blood sample were measured after randomization every 2 or 3 months during hospitalization for chemotherapy, and the geometric mean of these I/C ratios were analyzed. As continuous variables, there was significant negative correlation (coefficient = -0.33) between OS and I/C (Pearson Product Moment Correlation, $P=0.023$); there was significant negative correlation (coefficient = -0.31) between CRD and I/C (Pearson Product Moment Correlation, $P=0.045$) as well. I/C is a significant predictor of OS, CRD, and PFS (Figure 2E, 2F and 2G, respectively).

Multivariate analysis of predictive factors for OS, CRD, and PFS was performed using Cox regression models that included study arm, age, systemic risk, use of anti-insulin resistance medications (biguanides and/or thiazolidinediones), average glucose during chemotherapy, and I/C (Table 3). Factors which significantly predicted poor/short OS included the age ≥ 60

years ($P=0.0002$), I/C 0.175 ($P=0.0016$) and average glucose 180 mg/dL ($P=0.0236$). Similarly, factors that significantly predicted poor/short PFS included age 60 years ($P=0.0008$), I/C 0.175 ($P=0.0002$), high systemic risk ($P=0.0173$) and average glucose 180 mg/dL ($P=0.0249$). In contrast, I/C 0.175 was the only factor that significantly ($P=0.0042$) predicted a poor/short CRD. As estimated by the hazard ratios, patients with I/C 0.175 were 5.7 times more likely to die, 7.8 times more likely to relapse, and 7.5 times more likely to progressive disease and/or die than those with I/C < 0.175 . There was no significant correlation between age and I/C (Spearman Rank Order, $P=0.379$). In contrast to exogenous insulin usage, the use of metformin and/or thiazolidinediones during chemotherapy was a significant ($P=0.046$) predictor of good/long PFS. 62% of the patients taking metformin and/or thiazolidinediones during hyper-CVAD were on these medications before enrollment. Patients using metformin and/or thiazolidinediones during chemotherapy were 5.4 times less likely to die and/or relapse.

DISCUSSION

Despite improved glycemic control, the management of hyperglycemia and diabetes using an intensive insulin regimen as practiced in this study did not improve ALL clinical outcomes. Possible explanations include: 1) that the degree of glycemic improvement achieved in this study was not sufficient to improve ALL clinical outcomes, 2) that the conventional therapy (control arm) was receiving fairly aggressive treatment of hyperglycemia and the outcomes were in general better than for hyperglycemic patients reported in 2004 [7], 3) that an unidentified confounding factor antagonized the beneficial effects of improved glycemic control, 4) that hyperglycemia was not causally related to response to chemotherapy and mortality in ALL patients but insulin resistance (of which hyperglycemia and insulin usage are surrogate markers) was linked to ALL survival, and 5) that there was a detrimental effect of the intensive insulin regimen on ALL clinical outcomes, which nullified the benefits from improved glycemic control. Furthermore, potential improvement in outcomes in the intensive insulin arm may have been blunted by an older patient cohort in this arm than in the conventional treatment arm. However, our secondary data analysis provided evidence to suggest that insulin and insulin analogues may be detrimental to ALL clinical outcomes.

In our secondary analysis, we used two standard deviations above the mean of the ethnic group with the highest I/C [17] as a cutoff value (i.e., 0.175) to divide the ALL patients into two groups for analysis; a higher degree of exogenous insulin usage in the group with I/C 0.175 is implied compared with the group with I/C < 0.175 . Kaplan-Meier analysis showed that this surrogate marker of exogenous insulin usage is a significant predictor of poor clinical outcomes in hyperglycemic ALL patients (Figure 2E–G). Cox regression analysis (Table 3) showed that I/C 0.175 is a significant predictor of poor clinical outcomes after controlling for study arm, systemic risk classification, age, use of metformin and thiazolidinediones during chemotherapy, and glucose. Although it remains unknown whether there is a glucose threshold that portends a better clinical outcome, an average of random glucose during chemotherapy that is 180 mg/dL predicts poor overall survival and progression-free survival. The use of metformin and/or thiazolidinediones during hyper-CVAD predicts improved progression-free survival (Table 3).

The association of hyperglycemia with outcomes in ALL patients is multifactorial. Factors such as an altered metabolism that supports the proliferative state of leukemic cells [18] and impaired immune function [19] may contribute to early relapse. Hyperinsulinemia and increased levels of IGF-1 have also been shown to promote tumor growth in solid tumors [20–22]. Recently we demonstrated that different types of antidiabetic pharmacotherapy had a differential direct impact on breast and pancreatic cancer cells [23]. Metformin suppresses

malignant cells through activation of AMPK leading to inhibition of mTOR [23–27]. Thiazolidinedione PPAR γ ligands inhibit proliferation and induce apoptosis of cancer cells [23, 28, 29], and inhibit tumor angiogenesis and invasion [28, 30]. They attenuate signaling through the IGF-1R signaling pathway [31, 32] as PPAR γ activation upregulates the expression of PTEN, an inhibitor of signaling through AKT/mTOR [33]. These suggest that insulin and analogues are detrimental while metformin and thiazolidinediones are beneficial to the clinical outcomes of hyperglycemic ALL patients undergoing hyper-CVAD chemotherapy.

To our knowledge, this is the first randomized clinical trial that showed improving glycemic control with an intensive insulin regimen did not improve the clinical outcome of leukemia in ALL patients who were hyperglycemic during hyper-CVAD chemotherapy. While we need to learn more about the interactions of diabetes and antidiabetic pharmacotherapy with cancers in order to optimize the diabetes care of cancer patients, future research may seek confirmation of beneficial effects of biguanides and thiazolidinediones to the clinical outcomes of malignant diseases in prospective trials. These future studies will open the avenue to improve the clinical outcomes and survival of hyperglycemic ALL patients simply by making an informed choice of antidiabetic pharmacotherapy.

CONCLUSION

Because of the high dose of glucocorticoids in the hyper-CVAD combination regimen, hyperglycemia is commonly encountered in induction chemotherapy using this regimen. Hyperglycemia during hyper-CVAD chemotherapy is associated with poor outcomes of acute lymphoblastic leukemia (ALL). Our randomized trial was terminated early due to futility because at the pre-determined interim analysis point, the ALL clinical outcomes in the intensive insulin group were trending to be worse than the conventional control group despite improved glycemic control. Since the probability that the intensive insulin group can have better clinical outcomes than the control group was less than 1%, the Institutional Review Board terminated the study. Therefore, the primary conclusion of this study is that intensive insulin therapy as practiced using a combination of glargine and aspart does not improve the outcome of ALL patients with hyperglycemia during hyper-CVAD induction therapy despite improvement in glycemic control.

Secondary analysis revealed that molar insulin-to-C-peptide ratio (I/C) >0.175 (a surrogate measure of exogenous insulin usage) was associated with decreased overall survival, complete remission duration and progression-free survival (PFS) while metformin and/or thiazolidinedione usage were associated with increased PFS. In multivariate analyses, factors which significantly predicted short overall survival included age ≥ 60 years, I/C >0.175 and average glucose ≥ 180 mg/dL. Factors that significantly predicted short progression-free survival included age ≥ 60 years, I/C >0.175 , high systemic risk and average glucose ≥ 180 mg/dL. I/C >0.175 was the only significant ($P=0.0042$) factor that predicted short complete remission duration. The secondary analyses suggest that exogenous insulin may be associated with poor outcomes while metformin and thiazolidinediones may be associated with improved outcomes. These results support the need for future studies to examine whether the choice of anti-diabetic pharmacotherapy may influence ALL outcomes.

Acknowledgments

Financial Support: Novo Nordisk, Inc., Princeton, NJ; Ladies Leukemia League, Inc.; The University of Texas MD Anderson Cancer Center, Division of Internal Medicine Multidisciplinary Research Program

This paper is dedicated to our beloved deceased colleague Dr. Mary Ann Weiser. The clinical trial was originally conceived and initiated by Dr. Weiser who has passed away. This clinical trial was partially funded by grants from:

Novo Nordisk, Inc., Princeton, NJ (PI: M. Weiser, succeeded by K. Vu), Ladies Leukemia League, Inc. (PI: M. Weiser) and The University of Texas MD Anderson Cancer Center, Division of Internal Medicine Multidisciplinary Research Program (PI: M. Weiser, succeeded by S. C. Yeung; co-PI: M. Andreeff).

References

1. Nilsen TI, Vatten LJ. Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Br J Cancer*. 2001; 84:417–422. [PubMed: 11161410]
2. Verlato G, Zoppini G, Bonora E, Muggeo M. Mortality from site-specific malignancies in type 2 diabetic patients from Verona. *Diabetes Care*. 2003; 26:1047–1051. [PubMed: 12663571]
3. Richardson LC, Pollack LA. Therapy insight: Influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Pract Oncol*. 2005; 2:48–53. [PubMed: 16264856]
4. Coughlin SS, Calle EE, Teras LR, et al. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol*. 2004; 159:1160–1167. [PubMed: 15191933]
5. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, et al. Less aggressive treatment and worse overall survival in cancer patients with diabetes: A large population based analysis. *Int J Cancer*. 2007; 120:1986–1992. [PubMed: 17230509]
6. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol*. 2000; 18:547–561. [PubMed: 10653870]
7. Weiser MA, Cabanillas ME, Konopleva M, et al. Relation between the duration of remission and hyperglycemia during induction chemotherapy for acute lymphocytic leukemia with a hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate-cytarabine regimen. *Cancer*. 2004; 100:1179–1185. [PubMed: 15022284]
8. Umpierrez GE, Isaacs SD, Bazargan N, et al. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. *J Clin Endocrinol Metab*. 2002; 87:978–982. [PubMed: 11889147]
9. Laakso M. Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes*. 1999; 48:937–942. [PubMed: 10331395]
10. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *Jama*. 2002; 287:2563–2569. [PubMed: 12020338]
11. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993; 329:977–986. [PubMed: 8366922]
12. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008; 359:1577–1589. [PubMed: 18784090]
13. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005; 353:2643–2653. [PubMed: 16371630]
14. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001; 345:1359–1367. [PubMed: 11794168]
15. Vu K, Yeung SC, Thomas DA, et al. Effect of Tight Control of Blood Glucose during Hyper-CVAD Chemotherapy for Acute Lymphocytic Leukemia. *Blood*. 2008; 112:336.
16. Thomas DA, O'Brien S, Jorgensen JL, et al. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. *Blood*. 2009; 113:6330–6337. [PubMed: 18703706]
17. Chen X, Scholl TO. Ethnic differences in C-peptide/insulin/glucose dynamics in young pregnant women. *J Clin Endocrinol Metab*. 2002; 87:4642–4646. [PubMed: 12364450]
18. Boren J, Cascante M, Marin S, et al. Gleevec (STI571) influences metabolic enzyme activities and glucose carbon flow toward nucleic acid and fatty acid synthesis in myeloid tumor cells. *J Biol Chem*. 2001; 276:37747–37753. [PubMed: 11489902]

19. Bagdade JD, Root RK, Bulger RJ. Impaired leukocyte function in patients with poorly controlled diabetes. *Diabetes*. 1974; 23:9–15. [PubMed: 4809622]
20. Gapstur SM, Gann PH, Colangelo LA, et al. Postload plasma glucose concentration and 27-year prostate cancer mortality (United States). *Cancer Causes Control*. 2001; 12:763–772. [PubMed: 11562117]
21. Goodwin PJ, Ennis M, Pritchard KI, et al. Fasting insulin and outcome in early-stage breast cancer: results of a prospective cohort study. *J Clin Oncol*. 2002; 20:42–51. [PubMed: 11773152]
22. Meyerhardt JA, Catalano PJ, Haller DG, et al. Impact of diabetes mellitus on outcomes in patients with colon cancer. *J Clin Oncol*. 2003; 21:433–440. [PubMed: 12560431]
23. Feng YH, Velazquez-Torres G, Gully C, et al. The impact of type 2 diabetes and antidiabetic drugs on cancer cell growth. *J Cell Mol Med*. 2010
24. Dowling RJ, Zakikhani M, Fantus IG, et al. Metformin inhibits mammalian target of rapamycin-dependent translation initiation in breast cancer cells. *Cancer Res*. 2007; 67:10804–10812. [PubMed: 18006825]
25. Buzzai M, Jones RG, Amaravadi RK, et al. Systemic treatment with the antidiabetic drug metformin selectively impairs p53-deficient tumor cell growth. *Cancer Res*. 2007; 67:6745–6752. [PubMed: 17638885]
26. Isakovic A, Harhaji L, Stevanovic D, et al. Dual antiglioma action of metformin: cell cycle arrest and mitochondria-dependent apoptosis. *Cell Mol Life Sci*. 2007; 64:1290–1302. [PubMed: 17447005]
27. Wang LW, Li ZS, Zou DW, et al. Metformin induces apoptosis of pancreatic cancer cells. *World J Gastroenterol*. 2008; 14:7192–7198. [PubMed: 19084933]
28. Fenner MH, Elstner E. Peroxisome proliferator-activated receptor-gamma ligands for the treatment of breast cancer. *Expert Opin Investig Drugs*. 2005; 14:557–568.
29. Lyles BE, Akinyeke TO, Moss PE, Stewart LV. Thiazolidinediones regulate expression of cell cycle proteins in human prostate cancer cells via PPARgamma-dependent and PPARgamma-independent pathways. *Cell Cycle*. 2009; 8:268–277. [PubMed: 19164938]
30. Dong YW, Wang XP, Wu K. Suppression of pancreatic carcinoma growth by activating peroxisome proliferator-activated receptor gamma involves angiogenesis inhibition. *World J Gastroenterol*. 2009; 15:441–448. [PubMed: 19152448]
31. Papageorgiou E, Pitulis N, Manoussakis M, et al. Rosiglitazone attenuates insulin-like growth factor 1 receptor survival signaling in PC-3 cells. *Mol Med*. 2008; 14:403–411. [PubMed: 18475308]
32. Cantini G, Lombardi A, Piscitelli E, et al. Rosiglitazone inhibits adrenocortical cancer cell proliferation by interfering with the IGF-IR intracellular signaling. *PPAR Res*. 2008; 2008:904041. [PubMed: 18670617]
33. Teresi RE, Shaiu CW, Chen CS, et al. Increased PTEN expression due to transcriptional activation of PPARgamma by Lovastatin and Rosiglitazone. *Int J Cancer*. 2006; 118:2390–2398. [PubMed: 16425225]

CLINICAL PRACTICEPOINTS

- Because of the high dose of glucocorticoids in the hyper-CVAD combination regimen, hyperglycemia is commonly encountered in induction chemotherapy using this regimen. Hyperglycemia during hyper-CVAD chemotherapy is associated with poor outcomes of acute lymphoblastic leukemia (ALL).
- Intensive insulin therapy as practiced using a combination of glargine and aspart does not improve the outcome of ALL patients with hyperglycemia during hyper-CVAD induction therapy despite improvement in glycemic control.
- Future investigation will examine whether the choice of anti-diabetic pharmacotherapy may influence ALL outcomes, and identify insulin-sparing strategies for treating hyperglycemia and improve the clinical outcomes of ALL patients who are hyperglycemic during hyper-CVAD chemotherapy.

CONSORT 2010 Flow Diagram

Figure 1.
Clinical trial CONSORT flow diagram.

Figure 2. Improved glycemic control using an intensive insulin regimen does not improve survival and exogenous insulin is associated with adverse ALL outcome

A) The distribution of mean serum glucose levels by cycle is shown as box plots for each chemotherapy cycle. Conventional therapy group: green. Intensive insulin group: red. Solid dots represent outliers.

B) The OS was not significantly different between the two study arms (Kaplan-Meier analysis, log-rank test, $P=0.70$). The 1-yr survival probability was 80.0% in the conventional therapy arm and 65.4% in the intensive insulin arm.

C) Of the 51 patients, there were 28 patients that relapsed and/or died. The CRD was not significantly different between the two study arms (Kaplan-Meier analysis, log-rank test, $P=0.74$). The 1-yr CRD probability was 82.8% in the conventional therapy arm and 80.0% in the intensive insulin arm.

D) The PFS was not significantly different between the two study arms (Kaplan-Meier analysis, log-rank test, $P=0.34$). The 1-yr PFS probability was 76.0% in the conventional therapy arm and 65.4% in the intensive insulin arm.

E) The OS was significantly longer in patients with $I/C < 0.175$ than those with $I/C \geq 0.175$ (Kaplan-Meier analysis, log-rank test, $P=0.012$). Patients with $I/C \geq 0.175$ had 1-year OS of 44.4% compared to 81.6% in those with $I/C < 0.175$.

F) The CRD was significantly longer in patients with $I/C < 0.175$ than those with $I/C \geq 0.175$ (Kaplan-Meier analysis, log-rank test, $P=0.025$). Patients with $I/C \geq 0.175$ had a 1-year CRD of 50% compared to 88.4% in those with $I/C < 0.175$.

G) The PFS was significantly longer in patients with $I/C < 0.175$ than those with $I/C \geq 0.175$ (Kaplan-Meier analysis, log-rank test, $P=0.0048$). Patients with $I/C \geq 0.175$ had 1-year PFS of 33.3% compared to 80% in those with $I/C < 0.175$.

Table 1

Demographics/characteristics of study participants

	Control		Intervention		P
	N	Percent	N	Percent	
Total	25	--	26	--	
Age (years)					0.046
Min	17	--	18	--	
Median	46.0	--	57.5	--	
Max	70	--	85	--	
Race					0.884
Hispanic	10	40.0	9	34.6	
Other	1	4.0	1	3.9	
White	14	56.0	16	61.5	
Sex					0.573
Female	9	36.0	12	46.2	
Male	16	64.0	14	53.8	
Diagnosis					0.304
ALL	15	62.5	16	61.5	
Burkitts	1	4.2	3	11.5	
Ph+	3	12.5	6	23.1	
T-LL	3	12.5	0	0.0	
Other	2	8.37	1	3.8	
Pre-existing DM2	7	28	6	23	0.935
Prior use of metformin and/or thiazolidinediones	5	20	3	11	1.000
Use of metformin and/or thiazolidinediones during hyper-CVAD	8	32	5	19	0.469
Random serum glucose at baseline (mg/dL)					0.508
Min	78		80		
Median	118.5		104		
Max	372		323		
BMI					0.53
Min	20.8		18.7		

	Control		Intervention		P
	N	Percent	N	Percent	
Median	29.2		27.7		
Max	44.3		43.8		

Table 2

Comparisons between the Intervention Arm with the Control Arm

	Control	Intervention	P
N	25	26	--
Complete Response			
No	2	3	11.5
Yes	23	23	88.5
ICU Admission			1.000
No	17	17	65.4
Yes	8	9	34.6
Number Hospitalizations (Total) ¹			1.000
Min	2	1	--
Median	9	7.5	--
Max	12	16	--
Number Hosp with Infections ²			0.185
Min	0	0	--
Median	2	1	--
Max	4	7	--
Days of hospitalization (Total) ¹			0.355
Min	26	13	--
Median	53	50	--
Max	90	99	--
Days of hospitalization (Chemo) ³			0.692
Min	2	13	--
Median	38	34.5	--
Max	63	61	--
Days of hospitalization (Non-chemo) ⁴			0.386
Min	0	0	--
Median	13	11.5	--
Max	42	61	--

¹Total: Number of total hospitalization admissions or total days of hospitalization from start of study through consolidation therapy, including both chemotherapy and non-chemotherapy admissions and admissions due to infections

²Hosp with infections: hospitalized due to infection

³Chemo: specifically for the purpose of administration of chemotherapy

⁴Non-Chemo: not related to chemotherapy

Table 3
Cox regression analyses of survival of hyperglycemic acute lymphoblastic leukemia patients.

Variable	Overall Survival			Response Duration			Progression-Free Survival		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Study Arm	1.865	0.678	0.2273	0.812	0.262	2.519	2.303	0.948	5.594
Systemic Risk Classification	4.266	0.811	0.0868	6.682	0.755	59.170	7.024	1.412	34.947
Age 60	8.308	2.763	0.0002	1.800	0.521	6.223	4.887	1.931	12.369
Use of Metformin and/or Thiazolidinediones during Chemotherapy	0.204	0.036	0.0741	0.382	0.047	3.109	0.184	0.035	0.970
Average Glucose 180	9.144	1.346	0.0236	4.910	0.541	44.559	7.710	1.294	45.922
I/C Ratio 0.175	5.716	1.939	0.0016	7.815	1.914	31.904	7.528	2.585	21.920
									0.0002

Bold font indicates P<0.05.