A Phase I Study of Targeted, Dose-Escalated Intravenous Busulfan in Combination With Etoposide as Myeloablative Therapy for Autologous Stem Cell Transplantation in Acute Myeloid Leukemia

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Abstract

A phase I study of targeted, dose-escalated busulfan in combination with etoposide as myeloablative therapy for autologous hematopoietic stem cell transplantation in acute myeloid leukemia identified a busulfan area under the curve (AUC) target of 1400 μmol/min as the maximum clinically acceptable dose. This busulfan AUC target might be associated with improved relapse-free survival.

Background: Busulfan and etoposide have been used as myeloablative therapy for autologous hematopoietic stem cell transplantation (HSCT) in adults with acute myeloid leukemia (AML) for > 20 years. The use of targeted intravenous (I.V.) busulfan has significantly improved the tolerability and efficacy of this regimen. We designed a dose-escalation study to examine the maximum tolerated dose (MTD) of targeted I.V. busulfan with bolus etoposide as preparative therapy for autologous HSCT in AML. **Patients and Methods:** In this single-center, phase I study, adult AML patients received I.V. busulfan targeted to either an area under the curve (AUC) of 1250 (cohort 1) or 1400 (cohort 2) μmol/min over 16 doses. Dose adjustments based on plasma pharmacokinetics occurred before doses 2 and 11. Etoposide 60 mg/kg I.V. was administered 24 hours after the last busulfan dose and 3 days before stem cell infusion. **Results:** Twelve patients with intermediate-risk AML in first complete remission were treated. All patients in cohort 1 and 5 patients (83%) in cohort 2 were within 10% of the target AUC. The MTD was not reached, although Grade ≥ 3 mucositis occurred in 3 patients (50%) in cohort 1 and in 4 patients (66%) in cohort 2, limiting further dose escalation. Two-year relapse-free survival was 33% in cohort 1 versus 67% in cohort 2 ($P = .08$). **Conclusion:** Etoposide and targeted, dose-escalated I.V. busulfan as myeloablative therapy for autologous HSCT in AML is safe, with mucositis being the most significant toxicity. A phase II study is warranted to further evaluate the activity and safety of busulfan targeted to AUC 1400 μmol/min.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 6, 377-83 Published by Elsevier Inc.
Keywords: Acute Myelogenous Leukemia, Autologous transplant, High-dose chemotherapy, Pharmacokinetics, Phase I Clinical Trial

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Submitted: Sep 18, 2014; Revised: Jan 9, 2015; Accepted: Feb 3, 2015; Epub: Feb 14, 2015

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2152-2650/$ - see frontmatter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.clml.2015.02.016

Introduction

Although most patients with newly diagnosed acute myeloid leukemia (AML) achieve complete remission (CR) after initial chemotherapy, less than a third of patients remain disease-free at 5 years.[1] Depending on prognostic features such as karyotype and the presence of distinct molecular mutations, options for potentially curative therapy after remission might include consolidation chemotherapy alone, high-dose chemotherapy with autologous stem cell rescue (also known as autologous hematopoietic stem cell transplantation [HSCT]), or allogeneic HSCT.

Autologous HSCT has been a well tolerated and effective therapy option for patients with intermediate-risk AML in first remission. Although several studies demonstrated favorable rates of disease-free survival with autologous HSCT relative to conventional chemotherapy alone, rates of overall survival (OS) were not significantly different in 3 large, randomized studies, with disease relapse being the principal cause of treatment failure.[2-6] Although allogeneic HSCT has been shown to be the preferred curative treatment option for younger patients with AML, < 50% of patients are able to find a suitable donor or to meet criteria for proceeding to allogeneic HSCT.[7] Thus, autologous HSCT remains a reasonable alternative treatment option for many patients.

Multiple strategies to decrease relapse rates after autologous HSCT have been explored, including additional cycles of consolidation chemotherapy before the transplant procedure, ex vivo purging of leukemic blasts from autologous stem cell collections, dose intensification of conditioning regimens, and immunomodulation after transplant.[8-12] In this study, we hypothesized that dose intensification with targeted intravenous (I.V.) busulfan would be possible, and that busulfan intensification might improve treatment outcomes for patients with AML treated with autologous HSCT.

Since the initial advent of busulfan-based conditioning regimens for autologous HSCT in AML, 2 changes have significantly improved busulfan dosing—the development of an I.V. formulation and the use of pharmacokinetics (PK)-driven dose adjustments. A large body of evidence has demonstrated significant interpatient variation in serum busulfan PK, and that PK targeting of busulfan might result in decreased transplant-related toxicity and improved outcomes in the setting of allogeneic HSCT for AML.[13-15] PK-adjusted busulfan dosing has not been explored previously in the setting of autologous HSCT in AML. We thus conducted a phase I study to determine the maximum tolerated dose (MTD) of targeted, dose-escalated I.V. busulfan in combination with bolus etoposide as myeloablative therapy for autologous HSCT in AML.

Patients and Methods

This was a single center, open-label, phase I dose-escalation study of targeted I.V. busulfan and etoposide in adult patients with AML in CR. The study protocol was approved by the Ethics Committee at University of California, San Francisco and was conducted in accordance with the recommendations of Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent before participation in the study. Eligible patients included adults aged 18 to 69 years deemed appropriate candidates for postremission consolidation with high-dose chemotherapy and autologous stem cell rescue per our institutional standards, including Eastern Cooperative Oncology Group performance status ≤ 2 and normal organ function (serum creatinine < 2.0 mg/dL, total bilirubin < 2.0 mg/dL, aspartate aminotransferase and alkaline phosphatase < 3 times the upper limit of normal, cardiac ejection fraction $\geq 40\%$, and DLCO $\geq 40\%$ of predicted). Exclusion criteria included acute promyelocytic leukemia, previous myeloproliferative neoplasm, active central nervous system leukemia, and uncontrolled intercurrent illness including active infections requiring antimicrobial therapy.

Therapy

All patients received consolidation chemotherapy after remission consisting of etoposide 40 mg/kg I.V. continuously infused over 96 hours in combination with cytarabine 2000 mg/m^2 I.V. given every 12 hours for a total of 8 doses. Granulocyte colony stimulating factor 5 mg/kg was administered daily using subcutaneous injection beginning on day 14 after the initiation of chemotherapy, increased to 10 mg/kg daily when the total white blood cell count (WBC) exceeded 1000/μL, and continued at 10 mg/kg through collection. Peripheral blood stem cells were collected when the total WBC exceeded 10,000/μL or the peripheral CD34-positive (CD34$^+$) cells exceeded 15/μL. The target CD34$^+$ cell dose for collection was 5 to 10×10^6 cells per kilogram. A minimum of 3 weeks of rest was required after hospital discharge before proceeding to autologous HSCT.

The starting dose level of I.V. busulfan was 14.4 mg/kg for cohort 1 (C1) and 16 mg/kg for cohort 2 (C2). Dose 1 of busulfan was given as a single I.V. infusion over 2 hours on day −11 or −10 of autologous HSCT (dose = 0.9 mg/kg I.V. for C1 and 1 mg/kg for C2) and served as a test dose. Plasma samples for busulfan area under the curve (AUC) determination were drawn at 2, 3, 4, and 6 hours from the start of dose 1. Plasma samples were shipped to the Mayo Clinic Laboratories (Rochester, MN) and analyzed using a commercial liquid chromatography-tandem mass spectrometry assay.

The AUC was calculated using the linear trapezoidal rule with a noncompartmental approach. The dose 1 AUC was calculated using extrapolated area-to-time-infinity after the last measurable plasma concentration (AUCinf). The average steady-state busulfan plasma concentration was calculated as the observed AUC divided by the dosing interval. Busulfan dosing resumed on day −8 and was given every 6 hours for an additional 15 doses. Busulfan PK assessments were repeated for doses 4 and 12, with blood drawn immediately before infusion and then at 2, 3, 4, and 6 hours from the start of the infusion. The dose 4 and 12 AUC values were calculated from initiation of the dose to time 6 hours (AUC6). PK-guided dose adjustments were made before dose 2 based on the dose 1 busulfan AUC and the established steady state goals of 1250 μmol/min for C1 and 1400 μmol/min for C2. A standard formula for dose adjustments was used: adjusted dose (mg) = (actual dose [mg] × target AUC dose [μmol/min])/actual AUC (μmol/min). Dose adjustments were made for results that deviated from the target AUC by > 5%. An additional dose adjustment was made between doses 10 and 12 based on the predetermined AUC6 at dose 4. The standard formulas used for determining dose adjustment between