# Myeloablative Intravenous Pharmacokinetically Targeted Busulfan Plus Fludarabine As Conditioning for Allogeneic Hematopoietic Cell Transplantation in Patients With Non-Hodgkin Lymphoma

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## Abstract

**Traditional myeloablative conditioning regimens in allogeneic transplantation are associated with high non-relapse mortality (NRM). We present the results of the use of intravenous busulfan and fludarabine (BuFlu) in 60 patients with non-Hodgkin lymphoma (NHL). Our data show that BuFlu offers an alternative option when myeloablation is deemed necessary.**

**Background:** Mortality associated with allogeneic hematopoietic cell transplantation (allo-HCT) has limited its broader application in patients with non-Hodgkin lymphoma (NHL). Pharmacokinetic treatment with targeted intravenous busulfan combined with fludarabine (BuFlu) was developed as a preparative regimen for acute leukemia and myelodysplasia. Data from this regimen in lymphoid malignancies are limited. **Patients and Methods:** We assessed outcomes in 60 consecutive patients with various subtypes of NHL and a median age of 54 years (range, 27-68 years) who received allo-HCT with targeted intravenous BuFlu between December 2004 and August 2010. The median number of previous therapies was 3 (range, 1-8) and median time from diagnosis to HCT was 32 months (range, 4.5-177.5 months). **Results:** At conditioning, 28 (47%) patients had a complete response (CR). Graft versus host disease (GVHD) prophylaxis consisted of tacrolimus plus methotrexate in 65% of cases. Donors were matched/related (n = 32 [53%]), matched/unrelated (n = 21 [35%]), or mismatched/unrelated (n = 7 [12%]). All patients underwent grafting. The cumulative incidence of grade II/IV acute GVHD was 74% (grade III/IV was 20%). The 2-year cumulative incidence of moderate to severe chronic GVHD was 62%. Nonrelapse mortality (NRM) at 100 days and 3 years was 10% and 25%, respectively. The cumulative incidence of relapse was 27%. Three-year progression-free and overall survival for all patients was 47.8% and 55%, respectively. **Conclusion:** Targeted intravenous BuFlu is a relatively well tolerated regimen and offers an alternative option when myeloablation is deemed necessary in patients with NHL.

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## Introduction

Non-Hodgkin lymphoma (NHL) includes a diverse group of malignancies ranging from indolent low-grade disease to high-grade aggressive disease. Although autologous hematopoietic cell transplantation (HCT) is effective therapy for many patients with NHL, a significant proportion of patients do not achieve long-lasting remission because of histologic characteristics and chemosensitivity. Allogeneic hematopoietic cell transplantation (allo-HCT) eliminates the risk of infusing disease possibly present in an autologous graft and allows exploitation of the graft versus lymphoma effect mediated by donor T cells.[1] Allo-HCT using myeloablative conditioning (MAC) has been shown to result in a lower risk of relapse than does autologous HCT, based on nonrandomized comparisons, but at the expense of a higher nonrelapse mortality (NRM), ranging from 30% to 50%, which explains in part the lack of overall survival (OS) benefit.[2-6] Moreover, patients with NHL are commonly older, with associated comorbidities, and are heavily pretreated. Our bone marrow transplantation program began using the combination of fludarabine and intravenous busulfan (BuFlu) in 2004 as the preferred regimen for patients receiving allografts based on the encouragingly low NRM reported by De Lima et al in patients with acute myeloid leukemia and myelodysplastic syndrome.[7] Because of the extensive data published on the association between busulfan steady state concentrations and toxicity and efficacy, we use a dose-targeting approach based on pharmacokinetic (PK) modeling with the first dose of busulfan to achieve a prespecified area under the concentration time curve (area under the curve [AUC]) target. We have found this to be a safe regimen of administering a myeloablative dose of busulfan to patients with a wide variety of diseases.[8-10] We have extended this approach to patients with NHL, and here we present mature results in a successive cohort of patients.

## Patients and Methods

We performed a retrospective analysis of 60 consecutive patients older than 16 years of age with NHL of any histologic subtype. Pathologic review using the World Health Organization classification was completed in all cases. Patients were eligible for inclusion if they underwent allograft procedures between December 2004 and August 2010. All patients provided consent for long-term follow-up after HCT for an observational study approved by the University of South Florida Institutional Review Board. The same institutional review board approved this retrospective study, with waiver of patient consent.

Indications for allo-HCT included disease relapse after autologous transplantation, bone marrow involvement, inability to collect autologous peripheral blood stem cells, and high risk of relapse because of histologic characteristics, high International Prognostic Index score, or high number of previous lines of therapy. Patients were eligible for HCT according to institutional guidelines as follows: age older than 16 years, left ventricular ejection fraction $\geq$ 45%, forced expiratory volume in the first second of expiration ($FEV_1$), forced vital capacity (FVC), and diffusing capacity of lung for carbon monoxide (DLCO) $\geq$ 50% of predicted values, aspartate aminotransferase and alanine aminotransferase levels $<$ 3 times the upper limit of normal, creatinine clearance $\geq$ 50 mL/min, and Karnofsky performance status $\geq$ 60%.

Chemotherapy-sensitive disease was defined as the achievement of a partial response (PR) or complete response (CR) to a chemotherapy (or chemoimmunotherapy) regimen immediately before transplantation, according to Cheson et al.[11] Patient comorbidities were scored retrospectively according to the Hematopoietic Cell Transplant Comorbidity Index (HCT-CI).[12]

### *Conditioning and Supportive Care*

Patients received fludarabine 40 mg/m$^2$ intravenously once daily for 4 days with dose reduction for renal insufficiency per the manufacturer's guidelines, followed each day by intravenous busulfan over 3 hours. Details of busulfan PK-targeted dosing, PK assay methodology, and AUC determination have been previously published.[8-10] All patients received lorazepam for seizure prophylaxis beginning 24 hours before busulfan administration until 24 hours after the last busulfan dose. Ursodiol 600-900 mg per day was given to prevent hepatotoxicity. Graft versus host disease (GVHD) prophylaxis included tacrolimus plus methotrexate or mycophenolate mofetil or sirolimus.[13,14]

All patients received granulocyte-colony stimulating factor–mobilized T-cell–replete peripheral blood hematopoietic stem cells from a human leukocyte antigen (HLA)–identical sibling or unrelated donor, matched by high-resolution DNA typing for 8 of 8 or 7 of 8 HLA-A, HLA-B, HLA-C, or HLA-DRB1. Hematopoietic stem cells were infused at least 36 hours after completion of the last busulfan dose. Patients with mismatched unrelated donor grafts received rabbit antithymocyte globulin (Thymoglobulin; Genzyme Corporation, Cambridge, MA) at a dose of 1 mg/kg intravenously on day $-3$ followed by 3.25 mg/kg/d on day $-2$ and day $-1$. Antimicrobial prophylaxis was given based on current institutional standards, as previously described.[8-10] Granulocyte-colony stimulating factor was not administered after transplantation.

### *Definition of End Point*

Neutrophil recovery after transplantation was defined as the first of 3 consecutive days of neutrophil counts of at least $0.5 \times 10^9$/L and platelet recovery as the first of 3 consecutive days of platelet counts of at least $20 \times 10^9$/L without transfusion in the previous 7 days. Chimerism studies were performed using a polymerase chain reaction/short tandem repeat method on unsorted bone marrow samples and peripheral blood CD3/CD33 subsets isolated by fluorescence-activated cell sorting and subsequently analyzed for donor chimerism.[15] Busulfan-related toxicities (liver dysfunction, seizures, and interstitial pneumonitis) were evaluated in the first 100 days after transplantation by Common Terminology Criteria for Adverse Events, version 3 (CTCAE-3) (ctep.cancer.gov/protocolDevelopment/elctronic_applications/docs/ctcaev3.pdf). Hepatic venoocclusive disease/sinusoidal obstructive syndrome (VOD/SOS) was diagnosed and staged according to criteria set forth by Jones et al.[16] Acute and chronic GVHD was graded using consensus criteria.[17,18] Response to transplantation and progression of disease after allografting were defined by radiographic or morphologic criteria.[11]

### *Statistical Analysis*

Using the Kaplan-Meier method, OS was estimated from the date of transplantation to the date of death from any cause or date of last follow-up. Progression-free survival (PFS) was estimated from