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A Phase I Trial of High-Dose Clofarabine, Etoposide, and Cyclophosphamide and Autologous Peripheral Blood Stem Cell Transplantation in Patients with Primary Refractory and Relapsed and Refractory Non-Hodgkin Lymphoma

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Clofarabine has significant single-agent activity in patients with indolent and aggressive non-Hodgkin lymphoma and synergizes with DNA-damaging drugs. Treatment, however, may be associated with severe and prolonged myelosuppression. We conducted a phase I trial to determine the maximum tolerated dose (MTD) of clofarabine in combination with high-dose etoposide and cyclophosphamide followed by autologous peripheral blood stem cell transplantation in patients with refractory non-Hodgkin lymphoma (NHL). Patients received clofarabine at 30-70 mg/m^2/day on days −6 to −2 in successive cohorts, in combination with etoposide 60 mg/kg (day −8), and cyclophosphamide 100 mg/kg (day −6), followed by filgrastim-mobilized PBSC on day 0. Sixteen patients of median age 57 (range: 32-67) years with diffuse large B cell (n = 8), follicular (n = 5), or mantle cell (n = 3) lymphoma that was either primary refractory (n = 2) or relapsed and refractory (n = 14) were treated at 5 clofarabine dose levels: 30 (n = 3), 40 (n = 3), 50 (n = 3), 60 (n = 3), and 70 mg/m^2/day (n = 4) in combination with etoposide and cyclophosphamide. All patients had grade 4 neutropenia and thrombocytopenia. Grade 3-4 nonhematologic toxicity was evenly distributed across all 5 dose levels, and included diarrhea (n = 3), mucositis (n = 1), nausea (n = 1), reversible elevation of alanine aminotranferease/aspartate aminotransferase (AST/ALT) (n = 1) or bilirubin (n = 1), and hemorrhagic cystitis (n = 1); all resolved by day +30 following transplantation. The MTD was not reached. No treatment-related deaths occurred. At day +30, 13 patients achieved a complete remission (CR) or unconfirmed CR (CR_U), and 2 patients achieved a partial response, for an overall response rate of 94%. After a median follow-up of 691 days, the 1-year progression-free survival (PFS) and overall survival (OS) were 63% (95% confidence interval [CI]: 43%-91%) and 68% (95% CI: 49%-96%), respectively. We recommend clofarabine 70 mg/m^2/day × 5 days as a phase II dose in combination with high-dose etoposide and cyclophosphamide for further testing as a preparative regimen in NHL patients undergoing autologous PBSC transplantation.

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INTRODUCTION

High-dose chemotherapy and autologous stem cell transplantation (ASCT) remain the most efficacious therapy for patients with relapsed non-Hodgkin lymphoma (NHL), although only patients with chemosensitive disease appear to benefit the most [1]. Patients whose disease has never responded to therapy are almost never salvaged by ASCT, whereas patients whose relapsed disease is resistant to conventional-dose chemotherapy salvage have only a 15% to 20% chance of long-term disease-free survival (DFS) with

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transplantation [1,2]. The major cause of treatment failure of ASCT remains relapse, indicating the need for novel and more effective preparative regimens.

The preparative regimens of high-dose etoposide, cyclophosphamide, and either carmustine (BCNU), total-body irradiation (TBI), or busulfan have been commonly used in patients with relapsed or refractory lymphoma [3-5]. Etoposide and cyclophosphamide have documented single-agent activity in resistant lymphoma [6,7], and been shown to be synergistic in tumor models [8,9]. The extent of single-agent activity of high-dose BCNU or busulfan in lymphoma remains undocumented. Furthermore, high-dose BCNU has been associated with interstitial pneumonitis (IP) [10] and busulfan with a significant incidence of sinusoidal obstruction syndrome (SOS), particularly when combined with high-dose cyclophosphamide or TBI [11]. Finally, TBI-based regimens have also been associated with an increased risk of IP and post-transplant myelodysplasia in patients undergoing ASCT for lymphoma [12,13].

Clofarabine (2-chloro-2-fluoro-deoxy-9-D-arabinofuranosyladenine) is a second-generation, purine nucleoside antimetabolite approved for relapsed or refractory pediatric acute lymphoblastic leukemia. In addition to its clinical activity in patients with relapsed and/or refractory acute leukemia [14-16], recent studies have also shown significant single-agent activity in mature lymphoid malignancies, including chronic lymphocytic leukemia (CLL) as well as indolent and aggressive NHL [17-19]. Although pharmacodynamic studies have suggested that higher doses of clofarabine may be more efficacious with dose-dependent accumulation of the active metabolite clofarabine triphosphate in CLL cells [17], severe and prolonged myelosuppression has limited testing of high doses without stem cell support [18,19]. Furthermore, in vitro synergy between clofarabine and cyclophosphamide has been demonstrated against lymphoid cells, whereby clofarabine triphosphate, which inhibits DNA polymerases and ribonucleotide reductase, impedes DNA damage induced by cyclophosphamide and other DNA damaging agents resulting in enhanced apoptotic cell death [20-22].

Based on its significant antilymphoma activity, potential for dose-response effect, and its synergy with the DNA damaging agents such as cyclophosphamide and etoposide, we hypothesized that the combination of clofarabine, etoposide, and cyclophosphamide may be an effective, novel preparative regimen for patients with NHL undergoing ASCT, where the limitation of prolonged myelosuppression would be overcome with stem cell support. As an initial step in developing this regimen, we conducted a phase I clinical trial to determine the maximum tolerated dose (MTD) of clofarabine in combination with high-dose etoposide and cyclophosphamide followed by autologous peripheral blood stem cell (PBSC) transplantation in patients with relapsed or refractory NHL.

PATIENTS AND METHODS

Patient and Donor Eligibility

Patients were eligible if they had primary refractory or relapsed and refractory diffuse large B cell (DLBCL), mediastinal B cell, mantle cell lymphoma (MCL), or diffuse large cell transformation of an indolent lymphoma, or relapsed or refractory follicular lymphoma (FL) with high FL International Prognostic Index (FLIPI) [23]. Refractory disease was defined as failure to achieve at least a partial response to either first-line chemotherapy (primary refractory) or the last chemotherapy regimen if given for relapsed disease (relapsed and refractory). Patients were also required to be 18 to 70 years old, have a Karnofsky performance status of $\geq$70%, and have adequate organ function defined by a left ventricular ejection fraction >45%, corrected gas transfer (DLCO) >50%, estimated creatinine clearance >60 mL/min/1.73 m^2, and serum bilirubin, aminotranferease (AST), and aspartate aminotransferase (ALT) levels <2 $\times$ upper limits of normal. Patients were excluded if they had a prior autologous or allogeneic transplant, active central nervous system lymphoma, uncontrolled infection, or if they were seropositive for human immunodeficiency virus (HIV). Patients could receive only filgrastim-mobilized PBSC. The study was approved by the institutional review board of Indiana University-Purdue University Indianapolis. All patients and donors gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Study Design and Treatment Plan

All patients received the same doses of etoposide and cyclophosphamide, whereas the dose of clofarabine was escalated in successive cohorts of 3 to 6 patients (see below). Etoposide was administered as a single dose of 60 mg/kg (actual body weight) intravenously (i.v.) over 4 hours on day -8, and cyclophosphamide was administered at 100 mg/kg (lower of either actual or ideal body weight) i.v. over 1 hour on day -6. Clofarabine was administered as a daily 1-hour i.v. infusion for 5 days on days -6 to -2, with the dose escalated in 5 successive cohorts at the daily dose levels of 30 mg/kg, 40 mg/kg, 50 mg/kg, 60 mg/kg, and 70 mg/kg. Filgrastim-mobilized PBSC were infused on day 0. Filgrastim (5 μg/kg/day) was then administered from day +1 until neutrophil recovery to at least 5.0 $\times$ 10^9/L. PBSC were mobilized using filgrastim (10 μg/kg/day) for 4 days and continued until collection was complete. Leukapheresis (3-4 blood volumes) was commenced on day 5 and continued daily for a maximum of 4 days until