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A Pilot Study of Continuous Infusion of Mycophenolate Mofetil for Prophylaxis of Graft-versus-Host-Disease in Pediatric Patients

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Mycophenolate mofetil (MMF), an ester prodrug of mycophenolic acid (MPA), is used increasingly for graft-versus-host disease (GVHD) prophylaxis. Empiric fixed-dose-escalation strategies in pediatric hematopoietic cell transplantation (HCT) recipients have failed to achieve target MPA exposure. We evaluated the safety and feasibility of a pharmacokinetics-based dosing approach using a novel continuous infusion (CI) method of administration of MMF in pediatric HCT recipients. All patients received a myeloablative conditioning with cyclosporine A and MMF for GVHD prophylaxis. MMF was initiated on day 0 at a dose of 15 mg/kg every 8 hours. Based on steady-state pharmacokinetics, MMF was converted to CI to target a total MPA $AUC_{0\text{-}24}$ of 40 to 80 μg·hour/mL. The MMF dose was adjusted to maintain a total MPA steady-state concentration (C_{ss}) of 1.7 to 3.3 μg/mL. During the CI schedule, MPA $AUC_{0\text{-}24}$ was maintained at a mean of 40.1 μg·hour/mL (range, 20.6 to 63.8), and 17 of 19 patients (89%) achieved MPA C_{ss} within target of 1.7 to 3.3 μg/mL. Eighteen of 19 patients (95%) achieved neutrophil engraftment at a median of 13 days (range, 8 to 41) post-transplant and platelet engraftment at 39 days (range, 17 to 298) days post-transplant. Six of 18 assessable patients (33%) developed stages II to IV acute GVHD and 2 of 15 (13%) developed chronic GVHD. The MMF dose was reduced in 9 patients due to gastrointestinal symptoms (n = 6), low blood counts (n = 4), and viral infection (n = 3). Five patients with acute lymphoblastic leukemia relapsed, of whom 4 have died. Fifteen of 19 patients are alive with a median follow-up of 2.4 years (range, .4 to 4.9), with 3-year event-free and overall survival rates of 68% and 79%, respectively. In this pilot study of pharmacokinetically directed MMF dosing, we observed no toxic deaths, excellent engraftment, and low rates of grades III to IV acute and chronic GVHD. We found significantly lower half-life and higher drug clearance in pediatric HCT recipients compared with stable pediatric renal transplant patients or adult transplant patients. This regimen deserves further validation in a larger cohort of pediatric patients undergoing myeloablative transplantation.

INTRODUCTION

Graft-versus-host disease (GVHD) continues to be a major cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). Methods to prevent GVHD consist of administration of calcineurin inhibitor, either cyclosporine A or tacrolimus, and a second agent, such methotrexate. Despite the use of methotrexate/calcineurin inhibitor immunoprophylaxis, the rate of grades II to IV acute GVHD (aGVHD) remain high. Moreover, use of methotrexate

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post-transplant is associated with increased risk of mucositis, delay in time to myeloid engraftment, and potential pulmonary toxicity [1]. Therefore, a safer and more effective GVHD prophylaxis regimen is needed.

A combination of mycophenolate mofetil (MMF) and calcineurin inhibitor has been increasingly used for GVHD prophylaxis [2,3]. Use of MMF instead of methotrexate has been associated with a faster time to engraftment and reduced risk of mucositis [4]. Although the incidence of grades II to IV aGVHD appears to be similar, recent data, including a meta-analysis that compared MMF with methotrexate/calcineurin inhibitor, suggested a higher incidence of grades III to IV aGVHD with MMF [5,6].

MMF is an ester prodrug of mycophenolic acid (MPA). It is a purine analog, which interferes with the de novo pathway of nucleotide synthesis through inhibition of inosine monophosphate dehydrogenase (IMPDH), thereby inhibiting T and B cell proliferation. MMF is rapidly hydrolyzed to MPA by esterases in the systemic circulation, gut wall, and other tissues. MPA undergoes metabolism by UDP-glucuronosyltransferase to form the primary metabolite MPA glucuronide, which is inactive [7]. MPA glucuronide is secreted in the bile, and the deconjugated MPA is subject to enterohepatic circulation. The terminal disposition half-life in adult and pediatric solid organ transplant patients has been reported to be 8 to 12 hours [8]. Based on this, MMF or MPA is administered twice daily in adults. However, observation of a shorter half-life in HCT patients suggests the need for at least a thrice daily dosing of MMF/MPA in pediatric patients [9].

MMF dosing in pediatric HCT has been primarily extrapolated from data in solid organ transplant recipients, and the optimal dosing of MMF in the HCT setting has not been clearly defined. Exposure response relationships for MPA are much better defined in adult kidney recipients, in whom the established therapeutic goal is a total MPA $AUC_{0\text{-}12}$ of 30 to 60 μg·hour/mL or trough concentrations in the range of 1 to 3.5 μg/mL [10]. Pharmacokinetics studies suggest lower MPA exposure in HCT recipients, some as low as 30% to 50%, with standard starting MMF doses that are used in kidney transplant recipients [11-13]. After intravenous or oral administration of MMF to pediatric HCT patients, the plasma concentration reach values below 1 μg/mL within 4 hours, and very short half-lives have been observed. Low MPA trough levels have been associated with higher rates of aGVHD and graft rejection and lower response rates in the treatment of aGVHD [9,14,15].

Several strategies, including empiric fixed-dose escalation, have failed to achieve consistent MPA exposure, especially in the early post-transplant period after conditioning therapy [3]. Haentzschel et al. [16] demonstrated feasibility of MMF dosing to a targeted AUC in adult HCT recipients. However, increasing the dose of MMF leads to higher maximum MPA concentrations and may correspondingly lead to increased toxicity [17]. Increasing the frequency of dosing, given the short half-life, is also not very practical. An alternative novel method to administer MMF to achieve target MPA levels and avoid high peak level drug exposure is to use continuous infusion (CI), similar to the practice of administration of cyclosporine A and tacrolimus. In this report we describe the pharmacokinetics and clinical results of this MMF dosing approach in pediatric HCT recipients undergoing myeloablative transplantation.

METHODS

Enrollment

Subjects were enrolled in this pilot prospective trial at the Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center between December 2009 and May 2013. The study was approved by the University of Pittsburgh institutional review board and registered at www.clinicaltrials.gov (NCT01487577). Informed consent was obtained from the guardians, and assent or consent from patients in accordance with the Declaration of Helsinki.

Eligibility Criteria

Inclusion criteria were as follows: (1) age 6 months to 21 years; (2) myeloablative conditioning; (3) HLA-identical sibling donor, HLA-A, -B, -C, and -DRB1 allele-matched unrelated volunteer donor, or 4 of 6 HLA-A, -B, and -DRBb1 allele-matched cord blood unit; and (4) for cord blood units, minimum prefreezing nucleated cell dose of 3×10^7/kg for malignant diseases and 5×10^7/kg for nonmalignant diseases. Exclusion criteria were the following: (1) HIV infection or uncontrolled bacterial, viral, fungal, or other infection; (2) prior HCT within 12 months; (3) organ dysfunction defined as total serum bilirubin > 2.5 mg/dL or liver enzymes ≥ 5 times the upper limit of normal for age, glomerular filtration rate < 70 mL/min/1.73 m^2, left ventricular ejection fraction $\leq 40\%$, or shortening fraction $\leq 26\%$ and forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO) $\leq 50\%$ of predicted or if unable to perform pulmonary function tests, O_2 saturation $\leq 92\%$ of room air; and (4) Lansky or Karnofsky performance score $\leq 70\%$.

Conditioning Regimen and GVHD Prophylaxis

All patients received a myeloablative conditioning regimen of total body irradiation and cyclophosphamide or busulfan and cyclophosphamide. Patients receiving unrelated bone marrow donor or umbilical cord blood transplants received equine antithymocyte globulin (ATG) at a dose of 30 mg/kg/day for 3 days or fludarabine at a dose of 30 mg/m^2 a day for 5 days.

All patients received cyclosporine and MMF for GVHD prophylaxis. Intravenous cyclosporine was initiated on day −2 as a CI at a dose of 5 mg/kg/day and adjusted to maintain whole blood steady-state concentrations (C_{ss}) of 160 to 250 ng/mL as measured by the HPLC mass spectrometry method. Patients were converted to oral therapy when they tolerated oral intake and continued until at least day 100 when, in the absence of aGVHD, the dose of cyclosporine was tapered by approximately 10% per week through day 180.

MMF Dosing and Pharmacokinetics

Intravenous MMF was initiated at a dose of 15 mg/kg every 8 hours from day 0 and administered as a constant 2-hour infusion. The first MMF pharmacokinetics study was performed after a minimum of 5 doses to allow achievement of steady state. Serial blood samples were collected within 1 i.v. dosing interval just before (predose, 0 hour) and at 2, 3, 4, 5, 6, and 8 hours post-dose. Based on the total body clearance calculated from the i.v. pharmacokinetics study, MMF was administered as an i.v. CI of a solution of 10 mg/mL MMF in 5% dextrose in water, at an infusion rate (infusion rate = $C_{ss} \times$ total body clearance) to achieve a target total MPA $AUC_{0\text{-}24}$ of 40 to 80 μg·hour/mL. While on i.v. CI of MMF, total MPA levels were measured 3 times weekly and MMF dose adjusted to maintain a total MPA C_{ss} of 1.7 to 3.3 μg/mL. Oral dosing of MMF every 8 hours was initiated when patients were able to tolerate oral medications. The next pharmacokinetics study was performed after a minimum of 5 oral doses to allow the drug to reach steady state. Serial blood samples were collected over a single dosing interval just before (predose, 0 hour) and at .5, 1, 2, 3, 6, and 8 hours. While on oral MMF, total trough MPA levels were measured 3 times weekly, with dosing adjustments made to maintain a total MPA trough concentration (C_{trough}) of 1 to 3.5 μg/mL. MMF was continued until day 42 and, in the absence of aGVHD, tapered off over 8 weeks.

Safety Endpoint and Criteria for MMF Dose Modification

Key safety endpoints were day 100 transplant-related mortality, grades III to IV aGVHD, and neutrophil engraftment. Patients were monitored for any grade III or greater adverse events, using Common Terminology Criteria for Adverse Events (version 4.0).

Study guidelines for MMF dose reduction or discontinuation were based on BMT Clinical Trials Network trial 0802 (https://web.emmes.com/study/bmt2/protocol/0802_protocol/0802%20aGVHD_v3.pdf). These guidelines were as follows:

1. If gastrointestinal toxicity required medication for control of persistent vomiting or diarrhea (not related to GVHD), a dose reduction to 50% will be instituted, or if symptoms persisted and were severe