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A Phase I/II Study of Mycophenolate Mofetil in Combination with Cyclosporine for Prophylaxis of Acute Graft-versus-Host Disease after Myeloablative Conditioning and Allogeneic Hematopoietic Cell Transplantation

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ABSTRACT

In a phase I/II study, the combination of cyclosporine (CSP) and mycophenolate mofetil (MMF) was investigated as graft-versus-host disease (GVHD) prophylaxis after myeloablative conditioning and hematopoietic cell transplantation from an HLA-matched sibling donor. In phase I, 3 groups, each with 10 or 11 patients, received MMF (15 mg/kg) from day 0 to day 27 at decreasing dose intervals of every 12, 8, and 6 hours to determine a safe and effective total daily dose. At the 45 mg/kg/d dosage level, 4 of 11 patients developed only grade II GVHD, and a concentration at steady state of mycophenolic acid (the active moiety of MMF) consistent with a therapeutic range described for solid-organ transplantation was achieved. There was a suggestion of increased toxicity without improved efficacy at the 60 mg/kg/d dosage level. Accordingly, the 45 mg/kg/d dosage was therefore selected for phase II, and another 15 patients were added to this group from the phase I study (n = 26). The concentrations at steady state for this dosage at days 0, 6, 13, 20, and 27 were 2.73, 3.02, 3.20, 2.62, and 2.64 μg/mL, respectively. No toxicities were attributed to MMF at this dose. The median time to engraftment after hematopoietic cell transplantation was 15 days (range, 10-20 days). The incidence of acute GVHD was 62%, which was comparable to a group of historical controls receiving CSP and methotrexate (MTX) for GVHD prophylaxis. Although a significant improvement in the prevention of GVHD was not suggested, compared with CSP and MTX, MMF in combination with CSP could be considered in cases in which MTX is contraindicated.

KEY WORDS

Graft-versus-host disease • Cyclosporine • Mycophenolate mofetil

INTRODUCTION

Acute graft-versus-host disease (GVHD) contributes significantly to the morbidity and mortality associated with allogeneic hematopoietic cell transplantation (HCT) and limits its broader application to patients with nonmalignant and malignant diseases. The combination of cyclosporine (CSP) and methotrexate (MTX) is more effective than either agent alone for the prevention of acute GVHD [1,2]. Later studies documented that tacrolimus in combination with MTX was more effective than CSP and MTX for GVHD prophylaxis but that other outcomes, including overall survival, were no different between the 2 groups [3,4]. In many HCT programs, the combina-

tion of a calcineurin inhibitor with MTX has been adopted as the standard of practice for GVHD prophylaxis after allogeneic HCT. Although the combination of these immunosuppressive agents has reduced the incidence of acute GVHD, newer agents may further reduce the incidence or severity of acute GVHD and may avoid the toxicities associated with the previously used regimens. After allogeneic HCT, MTX is associated with delayed engraftment and an exacerbation of both oral and gastrointestinal toxicity. Moreover, the use of MTX is limited in patients with renal dysfunction or with significant "third spacing" including ascites or a pleural effusion.

Mycophenolate mofetil (MMF) is an ester prodrug of the immunosuppressant mycophenolic acid (MPA). After oral administration, MMF is rapidly hydrolyzed to MPA, which is a selective, reversible, and noncompetitive inhibitor of inosine monophosphate dehydrogenase (IMPDH). Inhibition of IMPDH blocks the de novo pathway of purine synthesis in T and B lymphocytes [5]. Phase III clinical studies of kidney transplantation have shown that MMF is effective in the prevention of graft rejection [6-8]. Preclinical studies of allogeneic HCT in a canine model have shown that MMF in combination with CSP has activity in preventing GVHD [9]. After myeloablative transplantation of marrow from unrelated dog leukocyte antigen-mismatched donors in a canine model of HCT, MMF synergized with CSP to prevent GVHD and improve survival. In the canine model of nonmyeloablative transplantation, the combination of CSP and MMF prevented graft rejection, and this combination is now commonly used after nonmyeloablative conditioning regimens for the prevention of graft rejection and GVHD [10-12]. There is a paucity of information regarding the effectiveness of MMF in preventing GVHD after myeloablative conditioning and allogeneic HCT. In a study of 14 patients receiving oral MMF with CSP, the maximum plasma concentrations (C_{max}) of MPA were lower than expected on the basis of pharmacokinetic data from healthy volunteers and solid-organ transplant patients, thus suggesting that an intravenous (IV) formulation may be beneficial to HCT patients [13]. The incidence of GVHD was not decreased relative to CSP and MTX [13]. Also of interest was that plasma MPA concentrations were also low when oral MMF was used for treatment of acute GVHD compared with levels achieved when it was used for the treatment of chronic GVHD [14]. On the basis of the demonstrated effectiveness of MMF for GVHD prevention in the preclinical study and the observation that MPA plasma levels were low after allogeneic HCT, a phase I/II study was conducted to evaluate the combination of CSP and MMF after a myeloablative conditioning regimen to identify a safe and effective dose of MMF.

PATIENTS AND METHODS

Patients

Between November 1999 and October 2002, 46 participants were enrolled in the study at the Fred Hutchinson Cancer Research Center (n = 29), Stanford University (n = 12), and City of Hope National Medical Center (n = 5). Data collection was completed and analyzed for safety and efficacy at 3 months. After 3 months, data collection was limited to the status of chronic GVHD, relapse, and survival. Patients 65 years of age or younger were eligible for study participation if they were scheduled to receive an unmodified hematopoietic cell graft from an HLA-identical sibling after a myeloablative conditioning regimen for advanced hematologic malignancies, multiple myeloma, or myelodysplastic syndrome. Advanced hematologic malignancies were defined for this study as acute myeloid leukemia or acute lymphocytic leukemia beyond a first complete remission (CR); secondary acute myeloid leukemia in first CR or beyond; chronic myelogenous leukemia in second chronic phase, accelerated phase, or blast crisis; and malignant lymphoma greater than second CR. Patients were excluded from the study if the estimated creatinine clearance was less than 60 mL/min or there was an abnormal liver function with total serum bilirubin greater than 1.5 times or aspartate aminotransferase/alanine aminotransferase greater than 2 times the upper limit of normal. Patients were also excluded if serology was positive for human immunodeficiency virus or if there were uncontrolled infections. The institutional review board at each center approved the study, and patients were registered on the study only after providing signed consent to confirm that they had been fully informed of the investigational purposes of the study.

Study Design

The study was an open-label multicenter phase I/II study of the combination of CSP and MMF for the prevention of acute GVHD after HCT from HLA-identical siblings. In the phase I part of the study, the MMF dose was escalated to determine the maximal effective but safe dose. Because the elimination half-life of the active metabolite MPA seemed shorter in HCT patients relative to solid-organ transplant patients, escalation of the total daily dose was achieved by decreasing the dosing interval from every 12 hours (group A) to every 8 hours (group B) and then to every 6 hours (group C). Pharmacokinetic studies of MPA were performed in all patients. At least 10 patients were accrued to each dose level, and an interim analysis was planned when the last patient included in that group had been followed up for 3 months. When an optimal dose was identified, the phase II part of the study was started, and 15 patients