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FK506 in Combination With Methotrexate for the Prevention of Graft-Versus-Host Disease After Marrow Transplantation From Matched Unrelated Donors

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The safety and potential efficacy of FK506 in combination with a short course of methotrexate (MTX) for the prevention of acute graft-versus-host disease (GVHD) after marrow transplantation from HLA-matched unrelated donors was evaluated in a single-arm Phase II study conducted at two centers. Forty-three patients, 15 to 54 (median 41) years of age, were transplanted for hematologic malignancies. Thirty-seven of 43 evaluable patients had evidence of sustained marrow engraftment. Five patients died before day 17 after transplantation. The median time to an absolute neutrophil count of $>0.5 \times 10^9$/L was 21 (range, 14 to 30) days. Nephrotoxicity (serum creatinine concentration >2 mg/dL or doubling of baseline) occurred in 32 patients (74% cumulative incidence during the first 100 days after transplant). Other adverse effects included hypertension (n = 27), hyperglycemia (n = 27), neurotoxicity (n = 9) and thrombotic thrombocytopenic purpura (n = 2). Severe veno-occlusive disease of the liver occurred in 9 (21%) of the 43 patients. Eighteen patients (42%) developed grades II to IV acute GVHD and five (12%) developed grades III to IV acute GVHD. Twelve of 25 evaluable patients developed extensive chronic GVHD within 1 year of marrow transplantation resulting in an estimate of the probability of developing this complication of 48%. The cumulative incidence of transplant-related mortality during the first 100 days was 37%. Kaplan-Meier estimates of disease-free survival at 2 years for good-risk, poor-risk, and all patients were 65%, 4%, and 32%, respectively. FK506 in combination with a short course of MTX appears active in preventing acute GVHD after marrow transplantation from unrelated donors. Further studies comparing the combination of FK506 and MTX with cyclosporine and MTX for the prevention of acute GVHD are warranted.
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ALLOGENEIC bone marrow transplantation is an effective therapy for a variety of lymphohematopoietic malignancies.[1-4] For patients who lack a suitable family member donor, HLA-matched unrelated donors are an alternative, and prolonged disease-free survival can be achieved.[5-9] However, the risks of developing acute and chronic graft-versus-host disease (GVHD) after a matched unrelated donor transplant are significantly higher than after a marrow transplant from an HLA-matched sibling.[7-13] The higher incidence of GVHD may be caused by disparities in major histocompatibility loci or by a greater degree of disparity in minor histocompatibility loci.[11] The combination of cyclosporine and a short course of methotrexate (MTX) is an effective pharmacologic regimen for prevention of GVHD after marrow transplantation from both HLA-matched siblings and from HLA-matched unrelated donors.[9,11-13] With this regimen, the incidence of acute grades II to IV GVHD after transplantation with unmanipulated marrow from an HLA-matched unrelated donor was 78%, and the incidence of grades III to IV acute GVHD was 36%.[11] In this setting, the incidence of chronic GVHD is 64%.[10] Because acute and chronic GVHD contribute to much of the morbidity and mortality associated with unrelated marrow transplantation, more effective prevention of these complications might improve outcomes.

The macrolide FK506 produced by *Streptomyces tsukubaensis* inhibits T-cell activation by forming a complex with FK binding protein-12, which blocks the seronine-threonine phosphatase activity of calcineurin.[14] This prevents the upregulation of interleukin-2 (IL-2) transcription mediated by NF-AT on the IL-2 gene promoter. FK506 has been demonstrated to be effective both for treatment and prevention of liver allograft rejection.[15-17] Preclinical studies showed that FK506 could prevent GVHD after marrow transplantation in rats and in dogs.[18,19] In the canine model, FK506 in combination with MTX was more effective than FK506 alone.[19]

Two pilot studies have evaluated the pharmacokinetics, safety, and efficacy of FK506, administered alone or in combination with methylprednisolone and MTX after transplantation from HLA-matched siblings.[20,21] In both studies, the most significant adverse effect of FK506 was nephrotoxicity, and the cumulative incidence of grades II to IV acute GVHD was estimated at 40% to 45%. Based on these results, we have carried out a Phase II study to evaluate the combination of FK506 and a short course of MTX for the prevention of GVHD in patients who received marrow transplants from HLA-matched unrelated donors.

MATERIALS AND METHODS

Patients. Patients were referred to the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle (n = 24) or Baylor University Medical Center in Dallas (n = 19) for treatment of hematologic malignancy between September 1992 and September 1994.

Patients were not eligible for the study if the estimated pretrans-

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Table 1. Patient Characteristics (n = 43)

		No. of Patients
Patient age (yr)		
Median (range)	41 (15-54)	
15-25		9
26-35		7
36-45		16
46-55		11
Male/female		27/16
Patient/donor gender match		
Male/male		10
Female/female		10
Male/female		17
Female/male		6
Donor compatibility		
Match		42
Mismatch (DR)		1
Diagnosis		
ALL 1st remission		3
relapse		2
AML 1st remission		2
relapse or evolution from myelodysplastic syndrome		13
CML Chronic or accelerated phase		8
blast crisis		1
Myelodysplastic syndrome		8
Multiple myeloma		6
Risk category		
Good		20
Poor		23
Conditioning regimens		
VP16/CY/TBI		15
BU/CY		11
CY/TBI		8
BU/TBI		6
BU/CY/modified TBI (myeloma)		2
Thiotepa/TBI		1

Abbreviations: BU, busulfan; CY, cyclophosphamide.

plant creatinine clearance was <60 mL/min, if the total bilirubin or SGOT/SGPT was >1.5 times the upper limit of normal, or if FCV or FEV was <70% of predicted. In addition, patients were excluded if they carried any of the human immunodeficiency viruses or received T-cell–depleted marrow. The risks and benefits of the treatment regimens were explained to each patient in detail, and written consent was obtained before hospital admission using forms approved by the Institutional Review Board.

Patient demographics and transplant characteristics are described in Table 1. The conditioning regimens included VP-16/cyclophosphamide (CY)/total body irradiation (TBI),[22] busulfan (BU)/CY,[23] CY/TBI, BU/TBI,[24] BU/CY/modified TBI, and thiotepa/TBI. The CY/TBI regimen consisted of the administration of CY (60 mg/kg of body weight) intravenously on two successive days and then either 1,320 cGy or 1,440 cGy of TBI in 11 or 12 fractions (120 cGy/fraction), respectively. For the purposes of this analysis, patients with acute lymphoid leukemia (ALL) or acute myeloid leukemia (AML) in first remission, chronic myelogenous leukemia (CML) in chronic or accelerated phase, and myelodysplastic syndromes (MDS) were categorized as good-risk. Patients with ALL or AML in relapse (marrow or central nervous system) or evolving from MDS, CML in blast crisis, and multiple myeloma were considered poor-risk.

Histocompatibility studies and donor selection. Criteria for donor selection required matching for the serologically defined private specificities encoded by HLA-A, B, and DR and recognized by the World Health Organization Nomenclature Committee for factors of the HLA system.[25] Typing for HLA-A and B antigens was performed according to the standard National Institutes of Health two-stage microcytotoxicity assay.[26] HLA-D region compatibility was defined as identity for DRB1 alleles determined by DNA hybridization with sequence-specific oligonucleotide probes.[27] One patient was mismatched at a single DRB1 locus (but within the same DR type).

GVHD prophylaxis. Treatment with FK506 was initiated on the day before transplantation and was continued for 6 months after transplant. The initial FK506 study dose (based on lean body weight) was 0.04 mg/kg/d as a continuous intravenous infusion. After 19 patients had been enrolled, the dose was reduced to 0.03 mg/kg/d because of concerns about nephrotoxicity. When patients had recovered from regimen-related gastrointestinal toxicity, FK506 was administered orally in two divided doses per day at five times the intravenous dose for the first nine patients and four times the intravenous dose for subsequent patients. The decision to decrease the dose was based on results of other ongoing studies in marrow and solid organ transplantation. The MTX dose was 15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11 after marrow transplantation.

The full dose of FK506 was administered until week 9 unless adverse effects or acute GVHD developed. Generally, if the serum creatinine doubled above baseline values or increased to levels above 2 mg/dL, the dose of FK506 was reduced or temporarily withheld. After week 9, if the patient had no evidence of GVHD, the FK506 dose was tapered until the drug was discontinued by week 26. In most cases, treatment with FK506 was stopped if relapse of hematologic malignancy occurred. FK506 steady-state blood levels during continuous intravenous infusion and trough levels during oral treatment were determined by enzyme-linked immunosorbent assay until the IMX assay became available.[28-30] Initially, an attempt was made to maintain FK506 whole blood levels in the range of 5 to 60 ng/mL. As data became available from larger studies in solid organ transplantation and from the concurrent marrow transplant study of patients with HLA-matched donors, FK506 levels were monitored and doses were adjusted to maintain whole blood concentrations in the range of 10 to 30 ng/mL.

Engraftment. Engraftment was defined as the first of two successive days after marrow transplantation with neutrophil counts >0.5 $\times$ 10^9/L. Patients were considered platelet and red blood cell-transfusion independent on the first of 30 consecutive days during which the patients did not require transfusions. The day of marrow infusion was designated as day 0. The first 20 patients received rhGM-CSF 250 μg/m^2 for the first 21 days after transplantation. This practice was discontinued when a recently completed Phase III placebo-controlled study failed to confirm the benefit of this practice.[31]

Adverse events. Nephrotoxicity was defined as a doubling of the baseline serum creatinine concentration or a serum creatinine concentration >2 mg/dL. This degree of renal dysfunction was defined as significant because doses of nephrotoxic agents such as FK506 were, in general, adjusted at this point. Severe veno-occlusive disease (VOD) has been previously defined.[32] Hypertension was defined as a diastolic blood pressure >90 mm Hg or a systolic blood pressure >140 mm Hg sustained for more than 3 consecutive days and requiring treatment. Hyperglycemia was defined as a serum glucose level >140 mg/dL and requiring treatment. Hyperlipidemia was defined as a serum total cholesterol concentration ≥240 mg/dL.

Assessment and treatment of GVHD. Acute and chronic GVHD

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were graded and staged by clinicians at the study centers using previously described criteria.[33,34] Patients with only persistent anorexia, nausea, or vomiting with a positive biopsy of the gastrointestinal tract were considered to be stage I gastrointestinal GVHD and were given an overall clinical score of grade II acute GVHD.[35,36] Biopsies were obtained when indicated to corroborate the clinical diagnosis of GVHD. Patients were censored for acute GVHD evaluation at the time of recurrent malignancy. Acute GVHD was treated with high-dose methylprednisolone (2 mg/kg/d) as previously described.[37] Some patients at the FHCRC were enrolled in protocols where methylprednisolone and oral nonabsorbable beclomethasone were administered for treatment of GVHD involving only the gastrointestinal tract (n = 2) or where a CD5-specific immunotoxin was given for treatment of systemic disease (n = 1).[38] Patients were evaluable for chronic GVHD if they survived 100 days after transplantation without relapse.[39,40] Chronic GVHD was treated with FK506 0.12 mg/kg/d orally divided in two doses 12 hours apart and prednisone at 1 mg/kg every other day. This regimen is similar to that previously reported for cyclosporine except that FK506 was administered daily instead of every other day.[39]

Statistics. The primary efficacy endpoint was the development of grades II-IV acute GVHD during the first 100 days after marrow transplantation. Cumulative incidence estimates were used to describe acute and chronic GVHD, nephrotoxicity and transplant-related mortality.[41] Kaplan-Meier estimates were used to describe disease-free survival.[42] Death or relapse without GVHD were considered as competing risks for the GVHD endpoints, and relapse was considered as a competing risk for the endpoint of transplant-related mortality.

RESULTS

Engraftment. Thirty-seven (86%) of 43 evaluable patients achieved a sustained granulocyte count $>0.5 \times 10^9$/L at a median of 21 (range, 14 to 30) days after transplantation. Five patients died before day 17. One patient who died on day 24 after marrow transplantation had a granulocyte count of 230×10^6/L. Of 31 patients who survived >50 days after transplant, 25 achieved platelet engraftment at a median of 35 days (range 13 to 100), and 25 achieved RBC engraftment at a median of 46 days (range 10 to 161) after marrow transplantation. The six patients who failed to achieve platelet or RBC engraftment died or relapsed before day 150.

Adverse effects. Nephrotoxicity was the most common adverse effect observed in the study. The cumulative incidence of nephrotoxicity during the first 100 days was 74%. Dialysis was required for seven patients (16%). Six of these seven patients required dialysis early posttransplant in association with other acute events, including sepsis, viral pneumonitis, pulmonary hemorrhage or VOD of the liver. The seventh patient who required dialysis had multiple myeloma with no other significant risk factors for renal failure. Nephrotoxicity not requiring dialysis generally occurred later after transplantation and improved after the FK506 dose was reduced.

The median peak serum bilirubin concentration during the first 28 days was 4.9 (range, 0.6 to 38.4) mg/dL. Nine (21%) patients developed severe VOD of the liver.[32] One patient who developed severe VOD of the liver had a previous autologous transplant. Three of six patients with multiple myeloma developed severe VOD of the liver. Hypertension

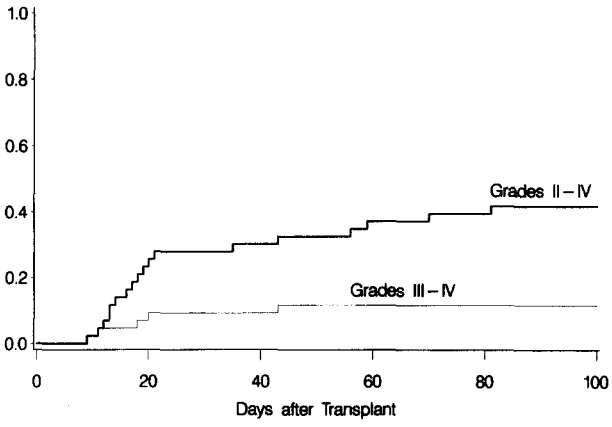

Fig 1. Cumulative incidence of grades II to IV and grades III to IV aGVHD during the first 100 days after marrow transplantation.

requiring treatment occurred in 27 (63%) patients. Three (7%) patients had hypertension before marrow transplantation. Nineteen (70%) of the patients who required treatment for hypertension had high-dose glucocorticoid treatment as a contributory cause. Hyperglycemia requiring therapy occurred in 30 (70%) patients. One patient had a history of insulin-dependent diabetes mellitus before transplantation. Nine (21%) developed hypercholesterolemia, and eight had high-dose glucocorticoid treatment as a contributory cause. Thrombotic thrombocytopenic purpura (TTP) occurred in two patients. In one, this complication occurred during treatment with cyclosporine after treatment with FK506 had been discontinued. One of the two patients with TTP had an intracranial hemorrhage. Neurologic adverse effects events were noted in another nine (21%) patients. Four patients had seizures. In one, the seizure recurred after treatment with FK506 had been discontinued. Three patients had headache during the intravenous infusion of FK506 requiring a decrease in the dose. Two patients had significant tremor, one had confusion, and one patient developed Guillain-Barré syndrome.

Acute GVHD. The cumulative incidence of grades II to IV acute GVHD was 42% (Fig 1). Two of the 18 patients with grades II to IV GVHD had biopsy-proven involvement of the upper GI tract manifested by anorexia, nausea, or vomiting without skin or liver involvement. Five (12%) of the 43 patients developed grades III to IV acute GVHD. All patients with grades II to IV acute GVHD received methylprednisolone or prednisone as first-line therapy. Five were enrolled in Phase III studies to determine if additional treatment with oral nonabsorbable beclomethasone or with a CD-5–specific immunotoxin improved the control of acute GVHD. Nine (50%) of 18 patients had a complete response to first-line treatment.

Chronic GVHD. Twenty-five patients who survived 100 days after marrow transplantation were considered at risk for chronic GVHD. Twelve developed extensive chronic GVHD requiring prolonged treatment with the combination of FK506 and prednisone. The estimate of the probability of developing chronic GVHD among those at risk is shown in

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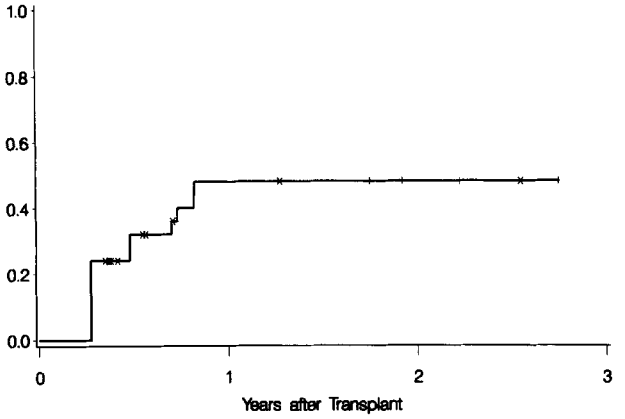

Fig 2. Cumulative incidence of clinical extensive chronic GVHD in 25 evaluable patients who survived without relapse beyond 100 days after transplantation. The "X" marks on the line are patients who died or relapsed without chronic GVHD. The "|" marks are patients alive without relapse or chronic GVHD.

Fig 2, where the estimate at 1 year and 2 years was 48%. Three of the 12 had de novo onset of chronic GVHD. Four had resolution of chronic GVHD and had immunosuppressive therapy stopped. Five remain alive with continued immunosuppressive therapy, and three died during continued treatment for chronic GVHD.

Relapse and survival. Seven patients had recurrent malignancy after transplant (Fig 3). All seven patients had advanced acute leukemia at the time of the transplant. Overall, 23 patients died of causes other than relapse (Table 2). Thirteen patients are currently alive in remission and have Karnofsky performance scores between 70% and 100% (median, 100%). Kaplan-Meier estimates of disease-free survival at 2 years are 32% (95% CI = 18% to 46%) for the entire group, 65% (95% CI = 44% to 86%) for patients with good-risk disease (n = 20) and 4% (95% CI = 0% to 13%) for patients with poor-risk disease (n = 23) (Fig 4).

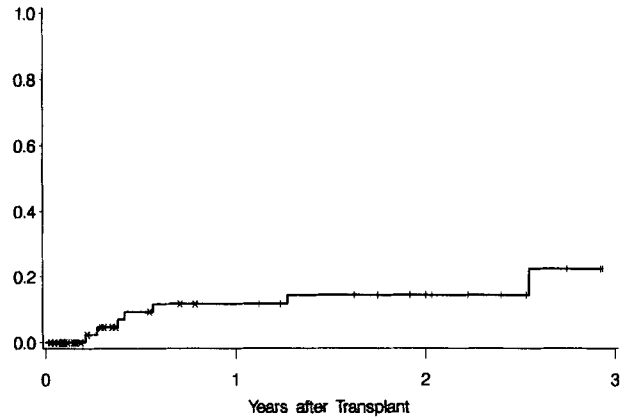

Fig 3. Cumulative incidence of relapse after marrow transplantation. The "X" marks on the line are patients who died without relapse. The "|" marks indicate patients alive and relapse-free at the time of analysis.

Table 2. Nonrelapse Mortality

	Primary Cause of Death	Patients	GVHD*
A. Organ failure			
Liver	VOD	8	3
Lung	Interstitial pneumonia†	2	
	Hemorrhage	2	1
Heart	Coronary artery disease	1	
B. Infections			
Lung	Aspergillus‡	5	2
	RSV	1	
CNS	Meningitis (Staph. Aureus)	1	
	Varicella-zoster encephalitis	1	
Sepsis	Candida	1	
C. GVHD			
GI	Hemorrhage	1	1
	TOTAL	23	7

* Active clinical GVHD at time of death.

† One patient had persistent Guillain-Barré syndrome.

‡ One patient also had CMV infection.

DISCUSSION

The most frequently used immunosuppressive prophylaxis after allogeneic marrow transplantation includes the combination of cyclosporine and a short course of MTX. Despite this approach, patients remain at considerable risk of acute and chronic GVHD and the resulting morbidity and mortality following transplantation from unrelated donors. This experience emphasizes the importance of investigating new immunosuppressive agents for GVHD prevention. The current trial is one of the first clinical studies to evaluate FK506 in unrelated marrow transplantation and extends the still limited clinical experience with the use of FK506 in combination with a short course of MTX.

The most frequent adverse effect noted in the present study was nephrotoxicity. FK506 causes constriction of preglomerular blood vessels, reducing renal blood flow and glomerular filtration.[43-45] Renal tubular cell damage and glomerular thromboses have also been reported.[46] Sodium depletion could potentiate FK506 nephrotoxicity as documented in rats.[47] The incidence of nephrotoxicity in the present study was similar to that described in the previous Phase II studies of FK506 in marrow transplantation from HLA-matched siblings.[20,21] Although FK506, like cyclosporine, is a known nephrotoxin, it has been previously reported that other complications such as VOD, sepsis, hypotension or use of Amphotericin B more closely correlate with the development of severe renal failure requiring hemodialysis.[48] Other common adverse effects were hypertension and hyperglycemia, which required treatment but did not have an adverse effect on overall outcome.

Severe neurologic complications have been uncommon in other studies evaluating the use of FK506 in marrow transplant patients. In this study, it was unclear if seizures were related to FK506. Patients were treated with anti-epileptic agents and the FK506 continued. Severe headaches only occurred in those patients receiving intravenous infusion of FK506. Headaches improved after reduction of the FK506

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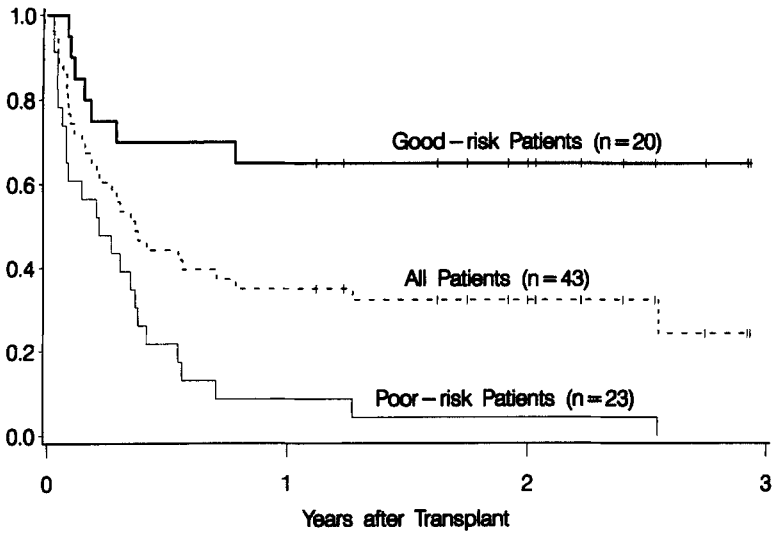

Fig 4. Kaplan-Meier estimate of disease-free survival in good-risk (n = 20), poor-risk (n = 23), and all 43 patients after marrow transplantation. The "|" marks are patients alive without relapse. The good-risk and poor-risk groups were those patients with less advanced or advanced hematologic malignancies, respectively.

dose.[20,21] One patient in this study developed Guillain-Barré syndrome which has been described after both autologous and allogeneic marrow transplantation.[49-54] This complication has not previously been associated with the use of FK506 in marrow transplant patients but has been reported in three patients receiving FK506 for prevention of graft rejection after liver transplantation.[55] Two of our patients developed TTP, a complication which has also been reported after both allogeneic and autologous stem cell transplantation. One of these patients had an intracranial hemorrhage. Neurologic complications are not common but are part of the syndrome, and occur as a result of the vascular injury. The inciting causes implicated in previous studies were radiation nephritis or treatment with cyclosporine and FK506.[21,56,57] After solid organ transplantation, TTP is often considered a complication of treatment with either cyclosporine or FK506.[58] The optimal management of TTP after allogeneic marrow transplant has not been established but usually consists of plasmapheresis and stopping, reducing, or changing immunosuppressive therapy.

Why might FK506 have a role in the management of GVHD and merit further investigation in the field of hematopoietic stem cell transplantation? Both cyclosporine and FK506 are considered to have their primary immunosuppressive effect through the inhibition of calcineurin phosphatase, even though these agents share no structural similarity. The observed nephrotoxicity and neurotoxicity are dose-dependent and similar in nature for both agents.[12,20,21,59,60] However, it is of interest that the clinical use of FK506 was first reported for successful salvage therapy in patients after liver transplantation who had rejection during prophylaxis with a cyclosporine-based regimen.[15] These findings have been confirmed in other studies.[61-65] In Phase III studies, liver and lung allograft recipients treated with FK506 and prednisone consistently had lower rates of acute graft rejection and a lower incidence of salvage therapy than patients treated with triple or quadruple regimens including cyclosporine, prednisone, azathioprine and ALG.[16,17,66] The reduced incidence of allograft rejection in the FK506 treatment groups was not necessarily associated with an increased incidence of severe toxicity when optimal dosing schedules were used.[18,67,68] In marrow transplant patients, calcineurin phosphatase activity was significantly suppressed in the peripheral blood mononuclear cells of patients treated with cyclosporine and was lower in the group with GVHD.[69] The authors concluded that if inhibition of calcineurin phosphatase is the only physiologic target of cyclosporine, further inhibition of calcineurin phosphatase activity alone might not be sufficient to control an alloreactive response. Since FK506 was first used successfully as salvage therapy in patients after liver transplantation who had failed a cyclosporine (CSP)-based regimen, there may be properties of the drug or activities other than inhibition of calcineurin phosphatase which could contribute to the improved outcome noted in these studies. Because there is currently a limited repertoire of effective immunosuppressive agents, further studies are of interest to determine if FK506 will have a role in the management of GVHD after allogeneic hematopoietic stem cell transplantation.

The 42% cumulative incidence of grades II to IV acute GVHD reported in this study compares favorably with the 78% incidence reported in previous studies with cyclosporine and MTX prophylaxis. Long-term disease-free survival in the current study was similar to the experience described recently for good-risk and poor-risk patients receiving cyclosporine and MTX.[9,70] Based on this experience and using the reduced dose of FK506 used in the latter half of this study, a Phase III study is in progress comparing the combination of FK506 and MTX with CSP and MTX for the prevention of acute GVHD after marrow transplantation from matched unrelated donors.

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