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Graft-versus-Host disease Prophylaxis with Everolimus and Tacrolimus Is Associated with a High Incidence of Sinusoidal Obstruction Syndrome and Microangiopathy: Results of the EVTAC Trial

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A calcineurin inhibitor combined with methotrexate is the standard prophylaxis for graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT). Everolimus, a derivative of sirolimus, seems to mediate antileukemia effects. We report on a combination of everolimus and tacrolimus in 24 patients (median age, 62 years) with either myelodysplastic syndrome (MDS; n = 17) or acute myeloid leukemia (AML; n = 7) undergoing intensive conditioning followed by HSCT from related (n = 4) or unrelated (n = 20) donors. All patients engrafted, and only 1 patient experienced grade IV mucositis. Nine patients (37%) developed acute grade II-IV GVHD, and 11 of 17 evaluable patients (64%) developed chronic extensive GVHD. Transplantation-associated microangiopathy (TMA) occurred in 7 patients (29%), with 2 cases of acute renal failure. The study was terminated prematurely because an additional 6 patients (25%) developed sinusoidal obstruction syndrome (SOS), which was fatal in 2 cases. With a median follow-up of 26 months, the 2-year overall survival rate was 47%. Although this new combination appears to be effective as a prophylactic regimen for acute GVHD, the incidence of TMA and SOS is considerably higher than seen with other regimens.

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INTRODUCTION

Beyond disease biology, the success of allogeneic hematopoietic stem cell transplantation (HSCT) in patients with hematologic malignancies is determined mainly by the occurrence and extent of graft-versus-host disease (GVHD) [1]. This is due to the close link between the extent of GVHD and nonrelapse mortality. In fact, patients who experience advanced GVHD have mostly limited survival [2]. Consequently, prevention of GVHD is the major goal and primary challenge in clinical HSCT. Although numerous trials have investigated various immunosuppressive drug combinations for GVHD prophylaxis, cyclosporin A (CsA) and methotrexate has remained the standard combination for more than 20 years [3]. The use of an alternative calcineurin inhibitor, tacrolimus, can significantly reduce acute, but not chronic, GVHD [4,5]. Despite these treatments, however, > 50% of patients who undergo HSCT develop clinically significant GVHD. In addition, methotrexate is highly toxic, inducing mucositis and delayed hematopoietic engraftment. Consequently, alternative immunosuppressive drug combinations have been investigated, including mycophenolate mofetil, but none has produced significantly better results [6,7].

Sirolimus (rapamycin), first found on Easter Island (Rapa Nui) as a naturally occurring compound isolated from a soil saprophyte, belongs to a new generation of immunosuppressive agents that inhibit the mammalian target of rapamycin (mTOR), an essential regulator of cell cycle in proliferating T cells. Sirolimus and tacrolimus (FK-506) act through different binding sites on a transcription factor–binding protein, FKBP-12, producing synergistic effects [8,9]. One advantage of using a combination of sirolimus and tacrolimus

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instead of CsA is the absence of interactions at the cytochrome level. A combination of sirolimus and CsA has been successfully used in patients after organ transplantation [10] and with tacrolimus after allogeneic matched related HSCT [11]. A short course of methotrexate was added in patients receiving grafts from unrelated donors [12], resulting in low rates of acute grade II-IV (26%) and chronic (42%) GVHD. Recently, methotrexate was successfully omitted, with no significantly change in the overall results [13].

Everolimus is a hydroxyethylester derivative of sirolimus that has a shorter half-life (22 vs 72 hours) and thus is more clinically manageable than sirolimus. It has been successfully used in combination with CsA after solid organ transplantation [14,15]. Like sirolimus [16,17], it exerts antiproliferative effects not only in T cells, but also in malignant cells, which theoretically could prevent disease recurrence after allogeneic HSCT [18,19]. Tacrolimus appears to be an ideal partner for everolimus in combination therapy, because it has minimal effects on serum everolimus levels compared with CsA. A pharmacokinetic interaction between CsA and everolimus has been described previously for healthy volunteers after single-dose administration, presumably originating from inhibition of hepatic cytochrome (CYP3A4) or P-glycoprotein efflux transporter. As a result, a higher dose of everolimus is needed in everolimus–tacrolimus combination therapy (EVTAC) than in everolimus–CsA combination therapy to achieve the desired everolimus blood level [20]. Given the potential synergism and favorable toxicity profile of EVTAC after allogeneic HSCT, we sought to investigate the efficacy of this combination in patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

METHODS

Study Design

The aim of this prospective pilot Phase II study was to evaluate EVTAC in the setting of allogeneic HSCT after busulfan-based intensive conditioning. All patients provided written informed consent, and the study design was approved by the local institutional review board and the German Federal Administration. Before recruitment, the study was registered at www.clinicaltrials.gov as NCT00117702. The trial's primary endpoint was the incidence and severity of acute GVHD, and secondary endpoints were the safety and incidence of chronic GVHD and infectious complications. A data safety monitoring board (DSMB) was installed to review toxicities. Inclusion criteria were hematologic malignancy, age 18 to 70 years, and adequate liver, renal, cardiac, and pulmonary function conferring eligibility for intensive busulfan-based conditioning. A patient could be included if a peripheral blood stem cell donor (either related or unrelated) with a maximum of 1 allele mismatch (9 out of 10) were available. DNA-based HLA typing of donor and recipient was performed using intermediate resolution for HLA class I (A, B, and C) and under high resolution for HLA class II (DRB1 and DQB1).

Study Therapy

Tacrolimus was administered either i.v. at a dose of 0.03 mg/kg/day or as a bioequivalent oral dose in 2 divided doses starting on the day before HSCT (day -1). The dose of tacrolimus was adjusted to maintain blood levels between 5 and 10 ng/mL. Starting on day 100 after HSCT, oral tacrolimus administration was tapered by 5% each week if GVHD was inactive. Everolimus was given orally starting on day 0 and a starting dose of 1.5 mg/day in 2 divided doses. The dose was subsequently adjusted to achieve a target blood concentration between 3 and 8 ng/mL. Everolimus administration was stopped on day 56 in the absence of uncontrolled GVHD. Serum concentrations of both drugs were obtained at least twice weekly. Acute and chronic GVHD were treated primarily with prednisone.

Tests for cytomegalovirus (CMV) pp65 antigen or polymerase chain reaction (PCR) for CMV DNA were performed weekly in patients at risk for CMV reactivation. In the event of a positive test result, preemptive therapy with valganciclovir was initiated and administered until day 100 or until PCR results were negative, whichever occurred last. Prophylaxis against infectious disease consisted of ciprofloxacin, fluconazole, and acyclovir.

DNA Extraction and Genotyping

To detect single-nucleotide polymorphisms (SNPs), DNA was extracted from whole blood using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol [21]. SNPs for glutathion-S-transferase (GST), such as GSTP1-Ile105Val, GSTA1*a/b, and Cyp3A4*1B polymorphisms, were detected by PCR–restriction fragment length polymorphism analysis, and null genotypes of GSTM1 and GSTT1 were detected by multiplex PCR as described previously [22,23]. Samples were genotyped for Cyp3A4*3, Cyp3A5*2, and Cyp3A5*3C polymorphisms (Cyp3A4*3: C_27535825_20, rs4986910; Cyp3A5*2: C_30633862_10, rs28365083; Cyp3A5*3C: C_26201809_30, rs776746) using a custom-designed system (Assay-on-Demand; Applied Biosystems, Darmstadt, Germany). In brief, a 10-ng DNA sample was added to a reaction volume of 15 μL containing 7.5 μL of TaqMan Universal PCR Master Mix, No AmpErase UNG, and 0.75 μL of custom-designed probe. Amplifications were performed on an Applied Biosystems 7500 real-time