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Low incidence of acute graft-versus-host disease with short-term tacrolimus in haploidentical hematopoietic stem cell transplantation

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ABSTRACT

Although tacrolimus (Tac) has immunosuppressive properties and exhibits promising efficacy against graft-versus-host disease (GVHD), little is known about Tac in the prophylaxis of GVHD after HLA-haploidentical hematopoietic stem cell transplantation (haplo-HSCT). In a multicenter randomized controlled trial, 174 patients received haplo-HSCT with GVHD prophylaxis involving short-term Tac (from −8 days to +30 days) or cyclosporine (CsA). The 100 day cumulative incidences of acute GVHD (aGVHD) and grade III–IV aGVHD with the short-term Tac regimen and CsA regimen were 29.1 (19.5–38.7)% vs. 50.0(39.6–60.4)% ($p = 0.005$) and 3.6(0.0–7.5)% vs. 13.5(6.1–20.9)% ($p = 0.027$), respectively. There were no significant differences in the incidences of chronic GVHD (cGVHD), relapse and cytomegalovirus infection. Lymphocyte subset analysis showed that T cells decreased to lower levels on the short-term Tac regimen within 3 months of transplantation. The disease-free survival and overall survival on the short-term Tac and CsA regimens were 59.3 (48.9–69.7)% vs. 55.7 (45.3–66.1)% ($p = 0.696$) and 65.1 (55.1–75.1)% vs. 61.4 (51.2–71.6)% ($p = 0.075$), respectively. Our findings indicate that the short-term Tac regimen for GVHD prophylaxis in patients undergoing haplo-HSCT is associated with a low incidence and slight severity of aGVHD and did not increase the incidence of relapse and cytomegalovirus infection.

1. Introduction

HLA-haploidentical hematopoietic stem cell transplantation (haplo-HSCT)has become an important transplantation technique for convenient donor selection in recent decades. However, the incidence of graft-versus-host disease (GVHD) in haplo-HSCT was higher than that of HLA-matched sibling HSCT [1,2]. The cumulative incidence within 100 days post-transplantation was 42.7-47.0% for grade II–IV acute GVHD (aGVHD) and 12.9–23.0% for grade III–IV aGVHD. The incidence of chronic GVHD (cGVHD) was 44.6–47.0%, with 20.0–21.3% for limited and 23.3–27.0% for extensive cGVHD [3–5]. The use of powerful post-transplantation GVHD prophylaxis with multiple immunosuppressive drugs has provided an approach to control allo-reactivity [6–8]. However, this method has resulted in delayed post-transplantation immune recovery and an increase in mortality due to infection and relapse.

In recent years, post-transplantation cyclophosphamide (PT-Cy) has been shown to be effective as the sole GVHD prophylaxis for myeloablative HLA-matched–related or unrelated BMT [9–11]. In 2015, data from Italy further revealed that PT-Cy and sirolimus-based GVHD prophylaxis could reduce the incidence of GVHD (cumulative incidences of grade II to IV and III–IV aGVHD were 15% and 7.5%, respectively, and the 1-year cumulative incidence of chronic GVHD was 20%). It was associated with a significant early increase in circulating regulatory T cells on day 15 after HSCT, with values <5% being predictive of subsequent GVHD occurrence [12]. Even so, there is still a need to explore new strategies to further reduce the incidence of GVHD.

Tacrolimus (Tac), a calcineurin inhibitor, has100-foldhigher in vitro inhibitory activity against T cells compared to that of cyclosporine (CsA) and has been used for the prophylaxis of GVHD

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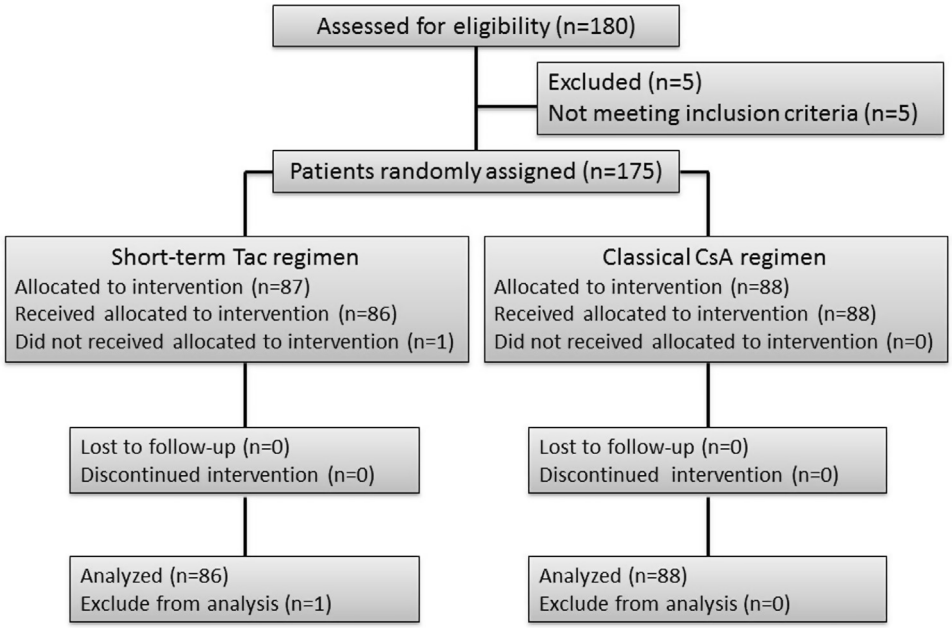

Fig. 1. Consort diagram. Flow of patients enrolled in the trial.

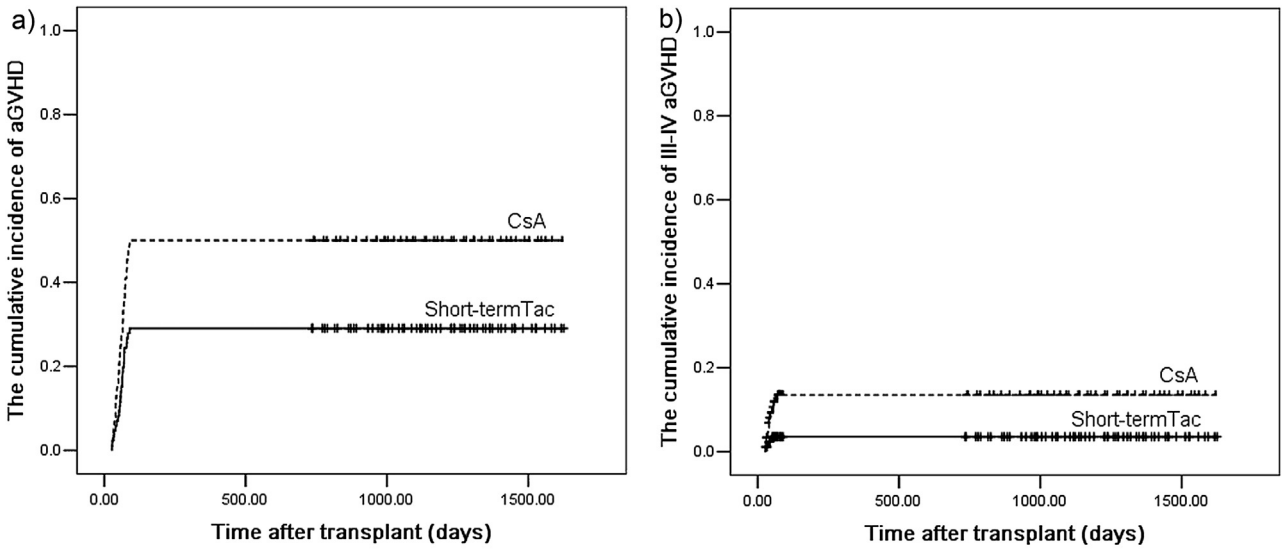

Fig. 2. Cumulative incidence of aGVHDwith the short-term Tac regimen (n = 86) and CsA regimen (n = 88). a: aGVHD; b: III–IV aGVHD.

both alone and in combination with other immunosuppressive agents in patients undergoing HLA-matched HSCT [13,14]. The correlations of Tac blood concentration with clinical efficacy and toxicity have also been studied sporadically since the introduction of Tac into clinical use [15,16]. Our previous retrospective single-arm studies demonstrated the feasibility of a decreasing stepwise regimen of Tac on the prophylaxis of GVHD in patients who underwent HSCT with HLA-haplo donors. However, the long-term use of Tac led to an increased incidence of infection, especially cytomegalovirus (CMV) infection [17].

Our goals in developing a short-term Tac regimen were the following: (1) to minimize the incidence of GVHD and to reduce the severity of GVHD; (2) to promote immune function recovery after transplantation; and (3) to reduce nephrotoxicity and neurotoxicity caused by continual administration of large doses of Tac. To achieve these three goals, we performed a multicenter, randomized open-label controlled study to investigate the efficacy, safety, and tolerability of short-term Tac combined with methotrexate (MTX) and mycophenolate mofetil (MMF) compared to a classical CsA + MTX + MMF regimen for the prophylaxis of GVHD in patients who underwent HSCT from HLA-haplo donors.

2. Patients and methods

2.1. Patients and study design

Between November 2010 and May 2013, 174 patients with hematological malignancies who underwent haplo-HSCT in three transplantation centers (Xinqiao Hospital, Third Military Medical University, Chongqing; General Hospital of Chengdu Military Region of PLA, Chengdu; and Affiliated Hospital of Kunming Medical College, Kunming)were enrolled in this study. The patients were