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Clinical Study Protocol

An Open-labeled, Multicenter Phase II Study of Tamibarotene in Patients with Steroid-refractory Chronic Graft-versus-Host Disease

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Chronic graft-versus-host disease (GVHD) is a major cause of late death and morbidity following allogeneic hematopoietic cell transplantation (HSCT). Retinoic acid (tamibarotene) exerts multiple effects on cell differentiation and is clinically used for the treatment of acute promyelocytic leukemia. Tamibarotene down-regulates both Th1 and Th17 differentiation in donor T cells after allogeneic HSCT, resulting in attenuation of experimental chronic GVHD. Based on preclinical data, we have launched a phase II study of tamibarotene in patients with steroid-refractory chronic GVHD. This study will clarify whether tamibarotene can exert beneficial effects in patients with steroid-refractory chronic GVHD.

Key words: Am80, tamibarotene, retinoid, chronic GVHD, steroid-refractory GVHD

Allogeneic hematopoietic stem cell transplantation (HSCT) is widely performed to treat many hematological malignancies, and a number of patients have now survived for years post-transplantation. However, allogeneic HSCT is frequently complicated by graft-versus-host disease (GVHD). GVHD can be divided into acute and chronic disease; chronic GVHD develops in approximately half of all long-term survivors of allogeneic HSCT [1]. Although steroids remain the standard initial treatment for chronic GVHD, and although half of all patients respond to first-line treatment, steroid-refractory chronic GVHD, especially generalized

scleroderma, has a poor prognosis. Chronic GVHD is currently the leading cause of long-term morbidity and mortality following allogeneic HSCT [1-4].

The pathogenesis of chronic GVHD remains elusive, but recent studies have provided some insights [4, 5]. Donor T cells play a central role in the immunological attack of host tissues seen in both acute and chronic GVHD. It was traditionally assumed that the predominant cytokines produced during acute GVHD are Th1 cytokines, whereas those produced during chronic GVHD are Th2 cytokines [6]. In addition to Th2 cells, recent studies have suggested that multiple cytokines secreted by Th1 and Th17 cells are involved

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in the pathogenesis of chronic GVHD [7–10].

Retinoid exerts multiple effects on cell differentiation and survival by binding to retinoic acid receptors (RARs) and retinoid X receptors [11]. Retinoic acids, such as all-trans-retinoic acid (ATRA) and tamibarotene (Am80), specifically target acute promyelocytic leukemia (APL) blasts *in vivo* and are clinically used as treatments for APL. In addition, retinoids can suppress Th17 cell differentiation with reciprocal induction of T regulatory cells [12]. Tamibarotene, a novel RAR α / β -specific synthetic retinoid, is approximately 10-fold more potent than ATRA and directly inhibits Th1 cytokine production [13,14]. We previously reported in an experimental mouse model that tamibarotene down-regulated both Th1 and Th17 differentiation in donor T cells, resulting in attenuation of chronic GVHD [8]. In the cited study, tamibarotene exhibited beneficial effects in terms of both the prevention and treatment of chronic GVHD.

Based on this background, we have launched an open-labeled, multicenter phase II study of tamibarotene in patients with steroid-refractory chronic GVHD.

Endpoints

The primary endpoints are the probability of failure-free survival (FFS) [15,16] and the complete/partial response rates at 24 weeks. Complete/partial responses will be assessed using the criteria of the National Institutes of Health (NIH) [17]. FFS will be defined by the absence of all of the following: any change in treatment, non-relapse mortality, and recurrent malignancy during the initial systemic treatment. Secondary outcome measures include the probability of FFS and the complete/partial response rates at 12 weeks, the probability of FFS and overall survival at 1 year after completion of 24 weeks treatment and the proportion of patients with FFS who exhibit at least a 50% reduction in the baseline steroid dose required at 24 weeks.

Study Design

This is a multicenter, prospective, non-randomized, trial to clarify whether tamibarotene can exert beneficial effects in patients with steroid-refractory chronic GVHD; no consensus has yet been attained on the optimal agents for secondary treatment of chronic

GVHD. Six facilities are participating in this study. (Trial registration number: UMIN registration number: 000020363)

Eligibility Criteria

All patients who meet the principal inclusion and exclusion criteria will be invited for screening. The principal inclusion and exclusion criteria are listed in Table 1. Written informed consent must be obtained by an investigator before any screening or inclusion procedure is conducted. This study is conducted in compliance with the principles of the Declaration of Helsinki, and the protocol has been approved by the institutional review board of each participating hospital. (Local Ethics Committee Board approval number: 250201)

Treatment Methods

The investigational agent, tamibarotene, is kindly provided by Toko Pharmaceutical Industrial Co., Ltd. Patients take tamibarotene orally (4 mg/day) for 24 weeks. If any unexpected adverse events with Grade 2 or expected adverse events with Grade 3 develop, the daily dose will be decreased to 2 mg/day, 2 mg every other day, or discontinued. The Common Terminology Criteria for Adverse Events version 4.0 indicate that patients with grade 3 liver dysfunction prior to registration, caused by chronic GVHD, can be treated without dose reduction or discontinuation. If the adverse events are mild (grade 0–1), the daily dose can be increased to 8 mg/day 4 weeks after the start of therapy. If a sufficient therapeutic effect is observed before the end of treatment, a maintenance dose of 2 mg/day until the end of the treatment is permitted.

Recurrent malignancy will be defined as hematological relapse or any unplanned intervention to prevent progression of malignancy in patients with molecular, cytogenetic, flow cytometric, or any other evidence of malignant disease after transplantation [15,16].

Sample Size

We assume the lower limit of interest to be 20% and the expected response rate to be 50% using historical control data on the rate of response to existing secondary treatments for chronic GVHD [18–27].

Using Simon's two-stage design model, we calculate that $p_0 = 0.2$, $p_a = 0.5$, first type I error (α) = 0.05 (one-sided), and second type I error (β) = 0.2. This yields an accrual number of 18 patients, using the normal approximation to the binomial distribution.

Interim Analysis

An interim analysis for inferiority will be performed once the first 9 patients are evaluable for primary endpoints. If, at the time of this interim analysis, two or less patients were found to have achieved FFS and the complete/partial response, the data and safety monitoring board will recommend early trial closure.

Discussion

Retinoids have been used to treat a variety of dermatological conditions, including scleroderma [28–30]. Because the skin manifestations of scleroderma are clinically and histologically similar to those of sclerodermatous chronic GVHD, retinoids have been used to treat chronic GVHD [31–33]. Marcellus et al. retrospectively evaluated the efficacy of a synthetic retinoid, etretinate, in 32 patients with refractory sclerodermatous chronic GVHD [32]. Clinical responses were assessed after 3 months of therapy, and 20 of 27 evaluable patients exhibited an improvement, including softening of the skin, flattening of cutaneous lesions, increased range of motion, and improved performance status. Many patients suffered skin breakdown and/or ulceration during therapy, leading to drug discontinuation in 6 patients.

As tamibarotene has little affinity for RAR γ , fewer adverse effects related to occupation of this receptor are expected compared with those caused by other retinoids, including etretinate. Although retinoids have been shown to inhibit the proliferation of normal human skin fibroblasts *in vitro* and to reduce collagen production, the precise mechanism of action of etretinate remains poorly understood [34–36]. A study in an experimental mouse model revealed the mechanism of action of tamibarotene [8]. Tamibarotene suppresses Th1 and Th17 responses and TGF- β expression in the skin, which are involved in the pathogenesis of chronic GVHD. Our planned study will clarify whether tamibarotene can safely exert beneficial effects in patients with steroid-refractory chronic GVHD.

Many different agents have been used as secondary treatments for chronic GVHD. However, the lack of standardized, validated response criteria has been a major obstacle when designing and interpreting clinical trials of such treatments. In the cited study on etretinate, Marcellus *et al.* assessed clinical responses in a unique manner. In efforts to unify response evaluations, the 2005 NIH Consensus Conference proposed new criteria for measurement of responses in clinical trials [17], and Inamoto *et al.* suggested FFS to be a meaningful endpoint for such trials [15,16]. In the planned study, the probability of FFS, and complete/partial responses assessed using the NIH criteria, will serve as the primary endpoints. To reduce the risk of steroid-related adverse events, we will also measure the proportion of patients who exhibit at least a 50% reduction in the required baseline steroid dose at 24 weeks.

We believe that this study will significantly contribute to the evolution of new secondary treatments for chronic GVHD.

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