Acta Med. Okayama, 2016
Vol. 70, No. 5, pp. 409-412

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Clinical Study Protocol

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

Yoshinobu Maeda[a]*, Hisakazu Nishimori[a], Yoshihiro Inamoto[b], Hirohisa Nakamae[c], Masashi Sawa[d], Yasuo Mori[e], Kazuteru Ohashi[f], Shin-ichiro Fujiwara[g], and Mitsune Tanimoto[a]

[a]*Department of Hematology and Oncology, Okayama University Hospital, Okayama 700-8558, Japan,*
[b]*Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo 104-0045, Japan,*
[c]*Department of Hematology, Osaka City University Hospital, Osaka 545-0051, Japan,*
[d]*Department of Hematology and Oncology, Anjo Kosei Hospital, Aichi 446-8602, Japan,*
[e]*Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka 812-0054, Japan,*
[f]*Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo 113-8677, Japan*
[g]*Division of Hematology, Department of Medicine, Jichi Medical University, Tochigi 329-0431, Japan*

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

Received June 29, 2016; accepted July 26, 2016.
*Corresponding author. Phone:+81-86-235-7227; Fax:+81-86-232-8226
E-mail:yosmaeda@md.okayama-u.ac.jp (Y. Maeda)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

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 RARα/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 p0 = 0.2, pa = 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 RARγ, 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.

Acknowledgments. The authors wish to acknowledge the coordinators and all other investigators who contributed/will contribute to this study. This protocol was written by YM, HN, and YI with the support of the Center for Innovative Clinical Medicine, Okayama University Hospital. HN, MS, YM, KO, SF, and MT took part in the trial design and set-up. This study is supported by the Japan Agency for Medical Research and Development (grant No. 15lk0103014h0003).

References

1. Socie G, Stone JV, Wingard JR, Weisdorf D, Henslee-Downey PJ, Bredeson C, Cahn JY, Passweg JR, Rowlings PA, Schouten HC, Kolb HJ and Klein JP: Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. N Engl J Med (1999) 341: 14–21.
2. Wingard JR, Majhail NS, Brazauskas R, Wang Z, Sobocinski KA, Jacobsohn D, Sorror ML, Horowitz MM, Bolwell B, Rizzo JD and Socie G: Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. J Clin Oncol (2011) 29: 2230–2239.
3. Martin PJ, Counts GW, Jr., Appelbaum FR, Lee SJ, Sanders JE, Deeg HJ, Flowers ME, Syrjala KL, Hansen JA, Storb RF and Storer BE: Life expectancy in patients surviving more than 5 years after hematopoietic cell transplantation. J Clin Oncol (2010) 28: 1011–1016.
4. Socie G and Ritz J: Current issues in chronic graft-versus-host disease. Blood (2014) 124: 374–384.
5. Nishimori H, Maeda Y and Tanimoto M: Chronic graft-versus-host disease: disease biology and novel therapeutic strategies. Acta Med Okayama (2013) 67: 1–8.
6. Coghill JM, Sarantopoulos S, Moran TP, Murphy WJ, Blazar BR and Serody JS: Effector CD4+ T cells, the cytokines they generate, and GVHD: something old and something new. Blood (2011) 117: 3268–3276.

7. Hill GR, Olver SD, Kuns RD, Varelias A, Raffelt NC, Don AL, Markey KA, Wilson YA, Smyth MJ, Iwakura Y, Tocker J, Clouston AD and Macdonald KP: Stem cell mobilization with G-CSF induces type 17 differentiation and promotes scleroderma. Blood (2010) 116: 819–828.
8. Nishimori H, Maeda Y, Teshima T, Sugiyama H, Kobayashi K, Yamasuji Y, Kadohisa S, Uryu H, Takeuchi K, Tanaka T, Yoshino T, Iwakura Y and Tanimoto M: Synthetic retinoid Am80 ameliorates chronic graft-versus-host disease by down-regulating Th1 and Th17. Blood (2012) 119: 285–295.
9. Broady R, Yu J, Chow V, Tantiworawit A, Kang C, Berg K, Martinka M, Ghoreishi M, Dutz J and Levings MK: Cutaneous GVHD is associated with the expansion of tissue-localized Th1 and not Th17 cells. Blood (2010) 116: 5748–5751.
10. Bruggen MC, Klein I, Greinix H, Bauer W, Kuzmina Z, Rabitsch W, Kalhs P, Petzelbauer P, Knobler R, Stingl G and Stary G: Diverse T-cell responses characterize the different manifestations of cutaneous graft-versus-host disease. Blood (2014) 123: 290–299.
11. Mark M, Ghyselinck NB and Chambon P: Function of retinoid nuclear receptors: lessons from genetic and pharmacological dissections of the retinoic acid signaling pathway during mouse embryogenesis. Annu Rev Pharmacol Toxicol (2006) 46: 451–480.
12. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M and Cheroutre H: Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science (2007) 317: 256–260.
13. Hashimoto Y, Kagechika H, Kawachi E, Fukasawa H, Saito G and Shudo K: Evaluation of differentiation-inducing activity of retinoids on human leukemia cell lines HL-60 and NB4. Biol Pharm Bull (1996) 19: 1322–1328.
14. Nagai H, Matsuura S, Bouda K, Takaoka Y, Wang T, Niwa S and Shudo K: Effect of Am-80, a synthetic derivative of retinoid, on experimental arthritis in mice. Pharmacology (1999) 58: 101–112.
15. Inamoto Y, Storer BE, Lee SJ, Carpenter PA, Sandmaier BM, Flowers ME and Martin PJ: Failure-free survival after second-line systemic treatment of chronic graft-versus-host disease. Blood (2013) 121: 2340–2346.
16. Inamoto Y, Flowers ME, Sandmaier BM, Aki SZ, Carpenter PA, Lee SJ, Storer BE and Martin PJ: Failure-free survival after initial systemic treatment of chronic graft-versus-host disease. Blood (2014) 124: 1363–1371.
17. Pavletic SZ, Martin P, Lee SJ, Mitchell S, Jacobsohn D, Cowen EW, Turner ML, Akpek G, Gilman A, McDonald G, Schubert M, Berger A, Bross P, Chien JW, Couriel D, Dunn JP, Fall-Dickson J, Farrell A, Flowers ME, Greinix H, Hirschfeld S, Gerber L, Kim S, Knobler R, Lachenbruch PA, Miller FW, Mittleman B, Papadopoulos E, Parsons SK, Przepiorka D, Robinson M, Ward M, Reeve B, Rider LG, Shulman H, Schultz KR, Weisdorf D and Vogelsang GB, Response Criteria Working G: Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biol Blood Marrow Transplant (2006) 12: 252–266.
18. Gilman AL, Chan KW, Mogul A, Morris C, Goldman FD, Boyer M, Cirenza E, Mazumder A, Gehan E, Cahill R, Frankel S and Schultz K: Hydroxychloroquine for the treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant (2000) 6: 327–334.
19. Browne PV, Weisdorf DJ, DeFor T, Miller WJ, Davies SM, Filipovich A, McGlave PB, Ramsay NK, Wagner J and Enright H: Response to thalidomide therapy in refractory chronic graft-versus-host disease. Bone Marrow Transplant (2000) 26: 865–869.
20. Akpek G, Lee SM, Anders V and Vogelsang GB: A high-dose pulse steroid regimen for controlling active chronic graft-versus-host disease. Biol Blood Marrow Transplant (2001) 7: 495–502.
21. Flowers ME, Apperley JF, van Besien K, Elmaagacli A, Grigg A, Reddy V, Bacigalupo A, Kolb HJ, Bouzas L, Michallet M, Prince HM, Knobler R, Parenti D, Gallo J and Greinix HT: A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. Blood (2008) 112: 2667–2674.
22. Olivieri A, Locatelli F, Zecca M, Sanna A, Cimminiello M, Raimondi R, Gini G, Mordini N, Balduzzi A, Leoni P, Gabrielli A and Bacigalupo A: Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood (2009) 114: 709–718.
23. Furlong T, Martin P, Flowers ME, Carnevale-Schianca F, Yatscoff R, Chauncey T, Appelbaum FR, Deeg HJ, Doney K, Witherspoon R, Storer B, Sullivan KM, Storb R and Nash RA: Therapy with mycophenolate mofetil for refractory acute and chronic GVHD. Bone Marrow Transplant (2009) 44: 739–748.
24. Kim SJ, Lee JW, Jung CW, Min CK, Cho B, Shin HJ, Chung JS, Kim H, Lee WS, Joo YD, Yang DH, Kook H, Kang HJ, Ahn HS, Yoon SS, Sohn SK, Min YH, Min WS, Park HS and Won JH: Weekly rituximab followed by monthly rituximab treatment for steroid-refractory chronic graft-versus-host disease: results from a prospective, multicenter, phase II study. Haematologica (2010) 95: 1935–1942.
25. Jedlickova Z, Burlakova I, Bug G, Baurmann H, Schwerdtfeger R and Schleuning M: Therapy of sclerodermatous chronic graft-versus-host disease with mammalian target of rapamycin inhibitors. Biol Blood Marrow Transplant (2011) 17: 657–663.
26. Weng JY, Du X, Geng SX, Peng YW, Wang Z, Lu ZS, Wu SJ, Luo CW, Guo R, Ling W, Deng CX, Liao PJ and Xiang AP: Mesenchymal stem cell as salvage treatment for refractory chronic GVHD. Bone Marrow Transplant (2010) 45: 1732–1740.
27. Pidala J, Kim J, Roman-Diaz J, Shapiro J, Nishihori T, Bookout R, Anasetti C and Kharfan-Dabaja MA: Pentostatin as rescue therapy for glucocorticoid-refractory acute and chronic graft-versus-host disease. Ann Transplant (2010) 15: 21–29.
28. Neuhofer J and Fritsch P: Treatment of localized scleroderma and lichen sclerosus with etretinate. Acta Derm Venereol (1984) 64: 171–174.
29. Shima T, Yamamoto Y, Ikeda T and Furukawa F: A patient with localized scleroderma successfully treated with etretinate. Case Rep Dermatol (2014) 6: 200–206.
30. Maurice PD, Bunker CB and Dowd PM: Isotretinoin in the treatment of systemic sclerosis. Br J Dermatol (1989) 121: 367–374.
31. Gryn J and Crilley P: Tretinoin for the treatment of cutaneous graft-versus-host disease. Bone Marrow Transplant (1990) 5: 279–280.
32. Marcellus DC, Altomonte VL, Farmer ER, Horn TD, Freemer CS, Grant J and Vogelsang GB: Etretinate therapy for refractory sclerodermatous chronic graft-versus-host disease. Blood (1999) 93: 66–70.
33. Ghoreschi K, Thomas P, Penovici M, Ullmann J, Sander CA, Ledderose G, Plewig G, Kolb HJ and Rocken M: PUVA-bath photochemotherapy and isotretinoin in sclerodermatous graft-versus-host disease. Eur J Dermatol (2008) 18: 667–670.
34. Jetten AM, Jetten ME, Shapiro SS and Poon JP: Characterization of the action of retinoids on mouse fibroblast cell lines. Exp Cell Res (1979) 119: 289–299.
35. Ohta A and Uitto J: Procollagen gene expression by scleroderma fibroblasts in culture. Inhibition of collagen production and reduction of pro alpha 1(I) and pro alpha 1(III) collagen messenger RNA steady-state levels by retinoids. Arthritis Rheum (1987) 30: 404–411.
36. Shigematsu T and Tajima S: Modulation of collagen synthesis and cell proliferation by retinoids in human skin fibroblasts. J Dermatol Sci (1995) 9: 142–145.