Oral Beclomethasone Dipropionate for the Treatment of Steroid-refractory Gastrointestinal Acute Graft-versus-host Disease

Sung-Eun Lee, M.D., Seok Lee, M.D., Ph.D., Byung-Sik Cho, M.D., Ki-Seong Eom, M.D., Ph.D., Yoo-Jin Kim, M.D., Ph.D., Hee-Je Kim, M.D., Ph.D., Chang-Ki Min, M.D., Ph.D., Seok-Goo Cho, M.D., Ph.D., Dong-Wook Kim, M.D., Ph.D., Jong-Wook Lee, M.D., Ph.D., Woo-Sung Min, M.D., Ph.D., Chong-Won Park, M.D., Ph.D. and Chun-Choo Kim, M.D., Ph.D.

Department of Hematology, Catholic Blood and Marrow Transplantation Center, College of Medicine, The Catholic University of Korea, Seoul, Korea

Acute graft-versus-host disease (GVHD) is one of the most severe complications following allogeneic stem cell transplantation (SCT), and involvement of the gut has been associated with increased mortality and a poorer response to high-dose systemic corticosteroids. For over a decade, oral beclomethasone dipropionate (BDP) has been studied in the treatment of acute gastrointestinal GVHD, as a monotherapy, or in combination with systemic corticosteroids. Here we report, for the first time in Korea, the efficacy of oral BDP (8 mg/day for 25 days) in 3 adults with acute lymphoblastic leukemia who developed steroid-refractory gastrointestinal GVHD (grade III) after myeloablative conditioning SCT (1 matched sibling transplant, 2 matched unrelated transplants). All patients responded completely to oral BDP treatment. Oral BDP is safe and effective for the control of steroid-refractory acute gastrointestinal GVHD. ***(Korean J Hematol 2009;44:304-309.)***

Key Words: Oral beclomethasone dipropionate, Allogeneic stem cell transplantation, Gastrointestinal acute graft-versus-host disease

INTRODUCTION

Allogeneic stem cell transplantation (SCT) has been an established treatment for various malignant and nonmalignant hematopoietic diseases. However, despite post-transplant immunosuppression, between 35% and 70% of patients still experience acute graft-versus-host disease (GVHD), with more than 35% of these patients requiring additional immunosuppressive therapy.[1] Systemic steroids are considered first-line treatment for acute GVHD; however, <50% of patients with grade II-IV acute GVHD achieve clinically relevant responses.[2] Patients with incomplete responses or failure to respond require an additional course of systemic steroids or other immunosuppressive drugs, which is associated with development of severe complications such as opportunistic infections. Incorporation of steroid-sparing regimens have been a critical issue, and for over a decade, oral beclomethasone dipropionate (BDP)

접수 : 2009년 9월 13일, 수정 : 2009년 9월 28일
승인 : 2009년 10월 2일
교신저자 : 이 석, 서울시 서초구 반포동 505
㉾ 137-701, 가톨릭대학교 의과대학 서울성모병원 조혈모세포이식센터 혈액내과
Tel: 02-2258-6055, Fax: 02-780-1283
E-mail: leeseok@catholic.ac.kr

Correspondence to : Seok Lee, M.D., Ph.D.
Department of Hematology, Catholic Blood and Marrow Transplantation Center, College of Medicine, The Catholic University of Korea
505, Banpo-dong, Seocho-gu, Seoul 137-701, Korea
Tel: +82-2-2258-6055, Fax: +82-2-780-1283
E-mail: leeseok@catholic.ac.kr

has been studied in the treatment of acute gastrointestinal GVHD, as a monotherapy or in combination with systemic corticosteroids.[3-5]

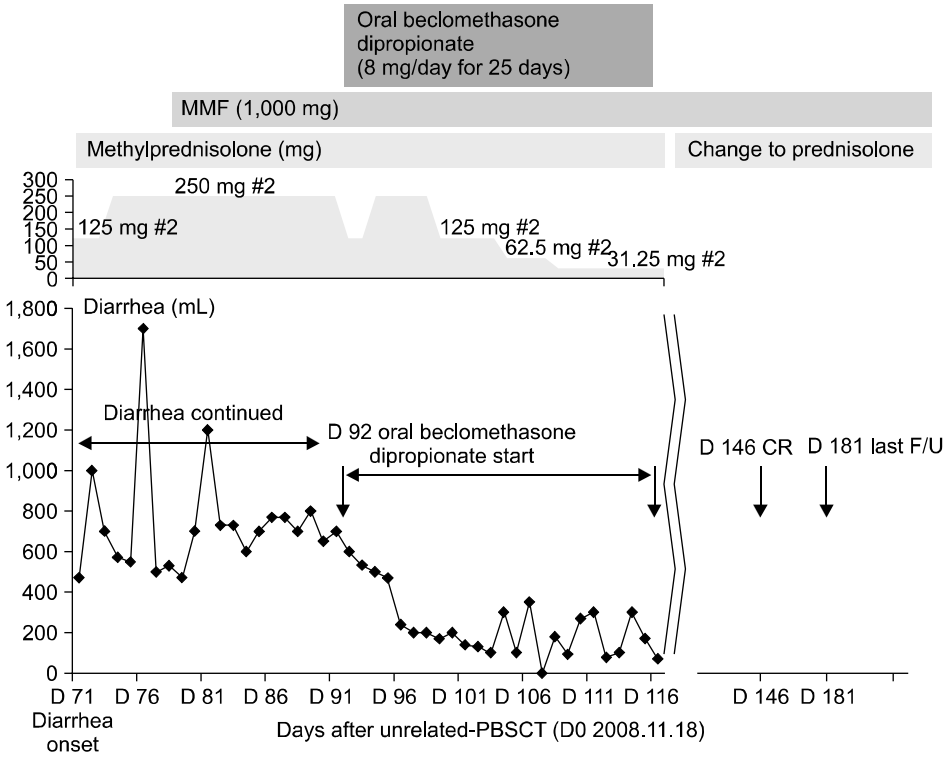
Oral BDP is a topically active corticosteroid with low absorption into the systemic circulation, which minimizes many of the deleterious side effects associated with systemic corticosteroids. Randomized trials have demonstrated that oral BDP is safe and effective in treating acute gastrointestinal GVHD when used with a short induction course of prednisone, reducing the risk of GVHD treatment failure and the risk of 1-year mortality after randomization.[4,5]

However, the efficacy of oral BDP has never been reported in Korea. Herein, we report on the efficacy of oral BDP (8 mg/day for 25 days) in 3 adults with acute lymphoblastic leukemia (ALL) who developed steroid-refractory gastrointestinal GVHD (grade III) after myeloablative conditioning SCT (1 matched sibling transplant, 2 matched unrelated transplants). Definitions for steroid-refractory gastrointestinal GVHD were as follows: (1) progression of GVHD after 3 days of steroid administration, (2) no clinical or biochemical changes after 7 days, or (3) incomplete response after 14 days of steroid treatment.[6]

CASE REPORT

1. Patient 1

A 26-year-old female with Philadelphia chromosome-positive ALL was transplanted from a fully matched, unrelated donor after complete induction and one cycle of a consolidation treatment course. The patient received unmodified peripheral blood stem cells following total body irradiation (TBI)-based myeloablative conditioning regimen (TBI 13.2 Gy + cyclophosphamide 120 mg/kg). GVHD prophylaxis was attempted by administra-



#: devided
MMF: mycophenolate mofetil
CR: complete response
F/U: flow up
D0: the day of stem cell transplantation

Fig. 1. Clinical course of grade III acute gastrointestinal GVHD in patient 1.

tion of tacrolimus plus a short course of standard dose methotrexate. The tacrolimus was controlled with maintenance of blood levels between 5 and 15 ng/mL. On day 71 following SCT, the patient developed acute gastrointestinal GVHD (grade III).

Sigmoidoscopy fiding showed patchy erythemas with pale colonic mucosa at S-colon with acute gastrointestinal GVHD histological features. Despite the use of methylprednisolone (2 mg/kg/day, i.v.) and the addition of mycophenolate mofetil (MMF; 1,000 mg/day, p.o.) after 7 days, the patient showed no response. Under the diagnosis of steroid-refractory acute gastrointestinal GVHD (grade III), oral BDP (8 mg/day for 25 days) was started on day 92 following SCT. The patient showed a gradual improvement in GVHD-related symptoms, and finally achieved a complete response (CR) on day 146 following SCT. At present, the patient is alive, and in a disease-free status (181 days after SCT) (Fig. 1).

2. Patient 2

A 38-year-old male with precursor B-ALL was transplanted from a fully matched sibling donor after complete induction and one cycle of consolidation treatment courses. The patient received unmodified bone marrow stem cells following a myeloablative conditioning regimen (TBI 13.2 Gy+cyclophosphamide 120 mg/kg). GVHD prophylaxis was attempted by administration of cyclosporine plus a short course of standard dose methotrexate. The cyclosporine was controlled with maintenance of blood levels between 150 and 300 ng/mL. On day 45 following SCT, the patient developed acute gastrointestinal GVHD (grade III). Sigmoidoscopy fiding showed a normal appearance but histological features were consistent with acute gastrointestinal GVHD. Despite the use of methylprednisolone (2 mg/kg/day, i.v.) and MMF (1,000 mg/day, p.o.), the patient showed no response. Under the diagnosis of steroid-refractory acute gastrointestinal GVHD (grade III), oral BDP (8 mg/day for 25 days) was started on day 59. The patient finally achieved CR on day 92 following SCT. At present, the patient is alive, and in a disease-free status (140 days after SCT) (Fig. 2).

3. Patient 3

A 15 year-old male with precursor B-ALL was transplanted from a fully matched, unrelated

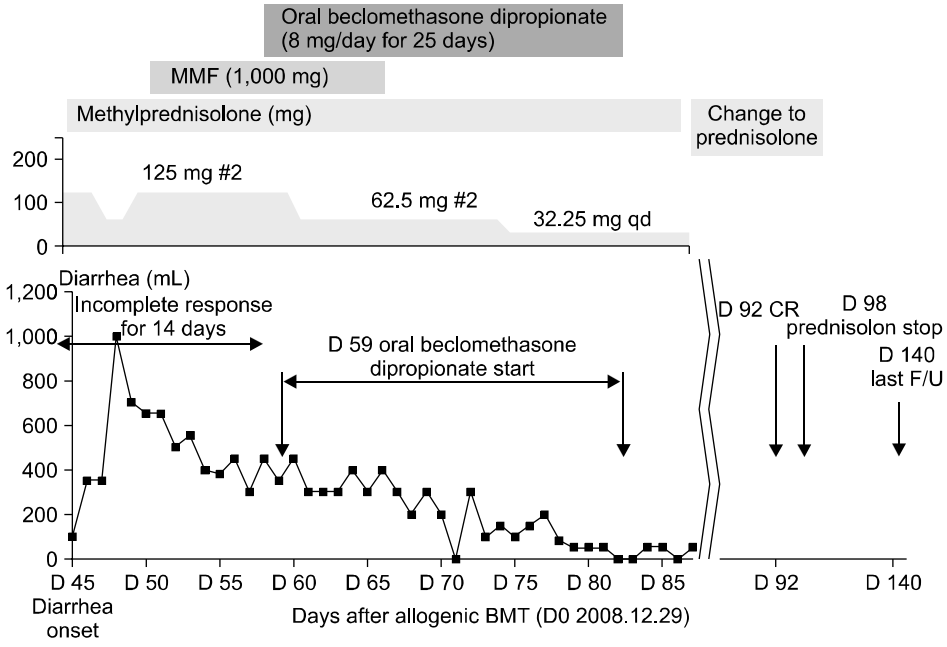


Fig. 2. Clinical course of grade III acute gastrointestinal GVHD in patient 2.

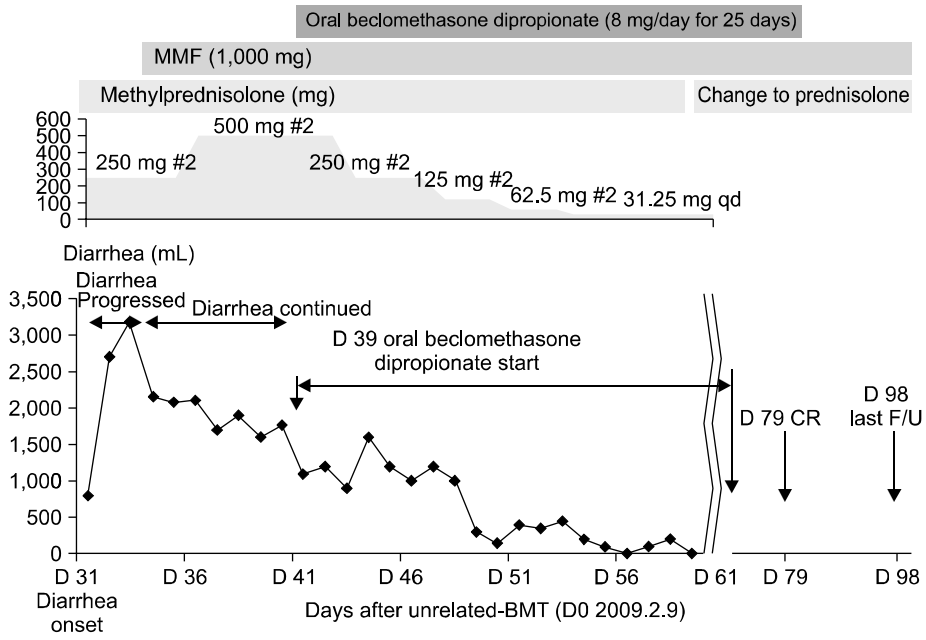


Fig. 3. Clinical course of grade III acute gastrointestial GVHD in patient 3.

donor after complete induction and one cycle of consolidation treatment courses. The patient received unmodified bone marrow stem cells following a myeloablative conditioning regimen (TBI 13.2 Gy+cyclophosphamide 120 mg/kg). GVHD prophylaxis was attempted by administering tacrolimus plus a short course of standard dose methotrexate. The tacrolimus was controlled with maintenance of blood levels between 5 and 15 ng/mL. On day 31 following SCT, the patient developed acute gastrointestinal GVHD (grade III). The colonic mucosa showed a normal appearance on sigmoidoscopy but histological features were consistent with acute gastrointestinal GVHD. Despite the use of methylprednisolone (8 mg/kg/day, i.v.) and MMF (1,000 mg/day, p.o.), the patient showed no response. Under the diagnosis of steroid-refractory acute gastrointestinal GVHD (grade III), oral BDP (8 mg/day for 25 days) was started on day 39. The patient finally achieved CR on day 79 following SCT. At present, the patient is alive, and in a disease-free status (98 days after SCT) (Fig. 3).

DISCUSSION

Systemic steroids are considered the gold standard in first-line treatment of acute GVHD, Unfortunately, $<50\%$ of patients with grade II-IV acute GVHD achieve continuing responses after initial therapy. Involvement of the gut is associated with a particularly poor response to high-dose systemic corticosteroids.[7] Treatment with an additional course of systemic steroids or other immunosuppressive drugs has limitations associated with development of severe complications, such as opportunistic infection, which lead to an increase in morbidity and mortality. Moreover, immunosuppressive drugs, including steroids, may also hamper the antileukemic effect of the graft. Therefore, whenever possible, acute GVHD should be managed using organ specific therapeutic approaches to avoid systemic effects.

In accordance with this strategy, several studies have demonstrated the efficacy and safety of oral BDP in the treatment of acute gastrointestinal GVHD, as a monotherapy, or in combination with systemic corticosteroids.[3-5] A phase I trial from the Fred Hutchinson Cancer Research Center showed that oral BDP (8 mg/day for up to 28 days) for the treatment of biopsy-proven mild-to-moderate acute gastrointestinal GVHD was safe and effective. The overall beneficial response was observed in 72% of 40 evaluable patients, and no

patient presented with severe infection or adrenal insufficiency.[3] This observation led to the subsequent design of phase II and III trials. In a randomized, placebo-controlled phase II study, the combination of oral BDP (8 mg/day for 30 days) and prednisone (1 mg/kg/day for 10 days) was more effective than prednisone alone as initial therapy for acute gastrointestinal GVHD (response rate; 71% versus 41%, P=0.021).[4] A multicenter randomized, placebo-controlled, phase III study demonstrated that oral BDP (total daily dose, 8 mg BDP for 50 days) is safe and effective in treating acute gastrointestinal GVHD when used with an induction course of 10 days of prednisone, allowing rapid tapering of prednisone with fewer recurrences of GVHD. In their study, the risk of GVHD treatment failure was reduced by $>$60%, and the risk of 1-year mortality after randomization by 45% in the oral BDP group.[5]

In Korea, however, no reports have demonstrated the efficacy of oral BDP in the setting of acute gastrointestinal GVHD. In our 3 cases, oral BDP (8 mg/day for 25 days) was added for control of steroid-refractory acute gastrointestinal GVHD (grade III). All patients were evaluated with an endoscopic mucosal biopsy and stool study in order to exclude infectious etiologies (e.g., cytomegalovirus enterocolitis). Despite the use of oral BDP for 25 days (due to a cost problem), patients' GVHD symptoms and signs were completely resolved, so that the dosage of systemic steroid could be tapered-off without flares of GVHD. Further long-term studies with a sizable population are needed to clarify the optimal patient criteria, as well as the optimal starting time and duration of oral BDP.

The beneficial effect of topical corticosteroids is a lower frequency of severe adverse events, including serious infections and clinical adrenal insufficiency. Oral BDP is metabolized in intestinal mucosa and the liver to beclomethasone-17-monopropionate, which has an approximately 25-fold greater glucocorticoid receptor binding activity than BDP; therefore, BDP does not appear in the systemic circulation. As a result of this metabolism, oral BDP is a topically active corticosteroid with low absorption into the systemic circulation, minimizing many of the deleterious side effects associated with systemic corticosteroids.[7,8] According to Baehr et al,[3] 60% of evaluable patients had biochemical evidence of adrenal axis suppression, but showed no clinical symptoms of adrenal insufficiency. Two recent studies on long-term use of oral BDP also demonstrated little evidence of clinical adrenal insufficiency.[5,9] Moreover, these studies demonstrated a lower incidence of activation of life-threatening infections in the oral BDP group. Although we did not check biochemical profiles of adrenal function, all 3 cases showed no evidence of clinical adrenal insufficiency or severe infection. In a phase IIII study, the only adverse events of erythema, arthralgia, cushingoid feature, dehydration, leukocytosis and hyperbilirubinemia were reported with higher incidence in the BDP group compared to placebo with a ratio superior to 1.5.[5]

In summary, oral BDP is safe and effective for control of steroid-refractory acute gastrointestinal GVHD. Our experience provides a rationale for incorporation of steroid-sparing regimens for control of acute gastrointestinal GVHD.

요 약

급성이식편대숙주반응은 동종조혈모세포이식의 심각한 합병증 중에 하나이며 특히 위장관 침범은 높은 사망률과 관계가 있고 스테로이드에 반응이 좋지 않다. 국외에서는 지난 10여년간, 경구 beclomethasone dipropionate (BDP)은 위장관 급성이식편대숙주반응에 단독 혹은 스테로이드와의 병합 치료로 연구되었다. 이에 저자들은 국내에서는 처음으로, 골수제거 전처치 후 조혈모세포이식(1 HLA 일치 형제간 이식, 2 HLA 일치 비혈연간 이식)을 시행했던 급성 림프구성 백혈병 환자 3명에서 발생한 스테로이드 불응성 위장관 급성이식편대 숙주반응(등급 III)에 대한 경구 BDP의 치료 효과를 보고하고자 한다. 모든 환자들은 경구 BDP을 이용한 치료 후 완전히 호전되

었다. 경구 BDP는 스테로이드 불응성 위장관 급성이식편대숙주반응에 안전하고 효과적이었다.

REFERENCES

1) Weissinger EM, Schiffer E, Hertenstein B, et al. Proteomic patterns predict acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Blood 2007;109:5511-9.
2) Deeg HJ. How I treat refractory acute GVHD. Blood 2007;109:4119-26.
3) Baehr PH, Levine DS, Bouvier ME, et al. Oral beclomethasone dipropionate for treatment of human intestinal graft-versus-host disease. Transplantation 1995;60:1231-8.
4) McDonald GB, Bouvier M, Hockenbery DM, et al. Oral beclomethasone dipropionate for treatment of intestinal graft-versus-host disease: a randomized controlled trial. Gastroenterology 1998;115:28-35.
5) Hockenbery DM, Cruickshank S, Rodell TC, et al. A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease. Blood 2007;109:4557-63.
6) Messina C, Faraci M, de Fazio V, Dini G, Calò MP, Calore E; EBMT Paediatric Working Party. Prevention and treatment of acute GvHD. Bone Marrow Transplant 2008;41(Suppl 2):S65-70.
7) Castilla C, Pérez-Simón JA, Sanchez-Guijo FM, et al. Oral beclomethasone dipropionate for the treatment of gastrointestinal acute graft-versus-host disease (GVHD). Biol Blood Marrow Transplant 2006;12:936-41.
8) Ibrahim RB, Abidi MH, Cronin SM, et al. Nonabsorbable corticosteroids use in the treatment of gastrointestinal graft-versus-host disease. Biol Blood Marrow Transplant 2009;15:395-405.
9) Iyer RV, Hahn T, Roy HN, et al. Long-term use of oral beclomethasone dipropionate for the treatment of gastrointestinal graft-versus- host disease. Biol Blood Marrow Transplant 2005;11:587-92.