BRIEF ARTICLES

Oral Beclomethasone Dipropionate for the Treatment of Gastrointestinal Chronic Graft-versus-Host Disease

Fernanda N. Villanueva, Jose Antonio Pérez-Simón, Fernando F. Silva, Teresa T. Caballero-Velázquez, Fermin F. Sánchez-Guijo, Conzuelo C. Cañizo, Lourdes L. Vázquez, Dolores D. Caballero, Jesús F. San Miguel

The most common approach for the treatment of chronic graft-versus-host disease (cGVHD) has been the long-term use of systemic steroids. Beclomethasone dipropionate (BDP) is a topically active corticosteroid with relatively low absorption from the gastrointestinal mucosa. It has been successfully used to treat acute GVHD (aGVHD), but its use in the cGVHD setting is far more limited. In the current study, BDP was administered to 33 patients who underwent allogeneic transplantation and had biopsy-proven gastrointestinal cGVHD (GI cGVHD). Twenty-six patients with GI cGVHD received BDP as first-line and 7 as either second- or third-line treatment. All patients received BDP together with a calcineurin inhibitor, except for 1 patient who was also receiving mycophenolate mofetil (MMF). BDP was administered for a minimum of 16 weeks and was tapered during 4 additional weeks. Of those patients receiving BDP as the first line of treatment, 22 (84.6%) achieved complete remission (CR) of GI cGVHD, 2 (7.7%) achieved a partial response (PR) and 2 (7.7%) did not respond or progressed. Median time to response was 28 days. Nevertheless, only 7 (27%) patients had maintained the response at last follow-up, whereas 19 (73%) finally relapsed or progressed. Median time to relapse was 147 days after the end of BDP. In the case of the patients who received BDP as a second- or third-line treatment, 3 (42.9%) achieved CR and 2 (28.6%) PR. For the whole series of patients, 13 patients (39.4%) were not receiving immunosuppressive treatment at final follow-up. Only 4 patients developed cytomegalovirus (CMV) reactivation, which was successfully treated with antiviral drugs. No fungal infection was observed during the treatment period. In conclusion, the current study shows that BDP, in the absence of systemic steroids, is a highly effective initial therapeutic approach for GI cGVHD, which helps to avoid complications related to systemic steroids.

Biol Blood Marrow Transplant 15: 1331-1336 (2009)

KEY WORDS: Gastrointestinal chronic graft-versus-hot disease, cGVHD, Beclomethasone dipropionate, BDP, Allogeneic stem cell transplantation

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a major complication after allogeneic hematopoietic stem cell transplantation (HSCT) [1]. Its incidence has increased over the past few years because of the older age of the patients, the use of peripheral blood as a source of progenitor cells, and the use of alternative donors [2].

Gastrointestinal (GI) GVHD affects up to 60% of patients after HSCT [3]. In the cGVHD setting, diagnostic features for the GI tract include esophageal web, stricture, or concentric rings documented by endoscopy or a barium contrast radiograph [4]. Symptoms of anorexia, nausea, vomiting, and diarrhea are not considered diagnostic of cGVHD, but are common symptoms in patients with the condition. Wasting syndrome can be a manifestation of cGVHD, but is often multifactorial and may result from decreased caloric intake, poor absorption, increased resting energy expenditures, and hypercatabolism, for example [5]. Intestinal involvement is usually more severe and difficult to treat compared with other target organs. In this regard, the Karnofsky score, presence of chronic diarrhea, weight loss, and skin involvement, allowed 3 subgroups of patients to be distinguished with respect to

From the Servicio de Hematología, Hospital Clínico Universitario de Salamanca y Centro de Investigación del Cáncer, Centro en Red de Medicina Regenerativa y Terapia Celular de Castilla y Leon, Salamanca, Spain.

Financial disclosure: See Acknowledgments on page 1335.

Correspondence and reprint requests: Jose A. Pérez-Simón, MD, PhD, Servicio de Hematología, Hospital Clínico Universitario, Paseo de San Vicente s/n, 37007 Salamanca Spain (e-mail: pesimo@usal.es).

Received March 25, 2009; accepted May 26, 2009

1083-8791/09/1510-0014$36.00/0
doi:10.1016/j.bbmt.2009.05.018

different survival in an International Bone and Marrow Transplant Research (IBMTR) study [6].

The most common approach for the treatment of cGVHD has been the use of prednisone. When used as a single agent, 3-year survival reported among high-risk patients [7], identified as those with extensive cGVHD plus thrombocytopenia, reached 26%. In this subset of patients, the addition of cyclosporine A (CsA) increased survival to 52% [8]. By contrast, the combination therapy did not improve the results of prednisone as a single agent among patients undergoing bone marrow transplantation (BMT) who developed standard-risk cGVHD [9]. The risks of this prolonged immunosuppression include viral and fungal infections, hypothalamic-pituitary-adrenal (HPA) axis suppression, myopathy, glucose intolerance, neuropsychiatric disease, and bone demineralization [10].

Beclomethasone dipropionate (BDP) is a topically active corticosteroid with relatively low absorption from the GI mucosa into systemic circulation compared with oral prednisone. BDP is metabolized in the intestinal mucosa and the liver. The active metabolite, 17-BMP, has an approximately 25-fold greater glucocorticoid-receptor binding activity than BDP [11,12]. In fact, BDP does not appear in the systemic circulation because of its metabolism in the intestinal mucosa and the liver, although 17-BMP can be detected in the blood stream [13,14]. Accordingly, adverse systemic effects are limited by incomplete absorption and intestinal hydrolysis of the propionate residues and by rapid clearance from the circulation [14,15]. Oral BDP has demonstrated activity in GI acute GVHD (aGVHD) [16,17] either alone [18] or in combination with prednisone at 1 mg/kg. In this patient population, BDP reduced the exposure to systemic corticosteroids, was associated with fewer infections and, possibly, preserved graft-versus-tumor (GVT) effects, yielding a statistically significant improvement in survival in a randomized, multicenter clinical trial [19].

Despite the deleterious effect of long-term exposure to systemic steroids in the cGVHD setting, the information available in the literature on the effectiveness of BDP in gastrointestinal cGVHD is limited to 13 patients. In this series of patients, BDP was shown to be safe and effective, although multiple courses might have been necessary to achieve or maintain response in some patients [20]. In the present report we describe the safety and efficacy of BDP as a treatment in a series of patients diagnosed with GI cGVHD.

MATERIALS AND METHODS

Patient Characteristics

BDP was administered to 33 patients who underwent allogeneic peripheral blood stem cell transplantation (PBSCT) and had biopsy-proven GI GVHD and clinical symptoms of cGVHD that developed after 100 days following transplantation. Patients were able to swallow medication and had confirmed negative stool cultures. Patient characteristics are summarized in Table 1.

Patients were classified according to National Institutes of Health (NIH) consensus criteria [21]. Diagnostic criteria were based on the clinical features, although confirmatory biopsies were available for all patients evaluated. No patient had esophageal involvement.

Twenty-six patients with GI cGVHD received BDP as first-line and 7 as either second- or third-line treatment. As before, symptoms consisted of nausea/vomiting in 13 patients, diarrhea in 12, anorexia and/or malabsorption plus weight loss in 9, and abdominal pain in 6 patients. As shown in Table 2, skin or mucosal involvement was also observed and, for these patients,

Table 1. Patients and Transplant Characteristics

	Patient characteristics (N = 33)
Age	
median (range)	33 (18-56)
CD34 cell dose	
median (range)	5.35 (1-6.26)
Diagnosis:	
AML	11
ALL	3
CML	2
CLL	3
MDS	4
NHL	6
HD	1
MM	2
Others	1
Disease status at transplant	
First CR	15
≥2nd CR	5
Chronic phase	2
Partial response	6
Refractory/progressive disease	2
Untreated	2
Others	1
Sex	
Male/female	20 / 13
Type of donor	
Related	21
Unrelated	11
Cord blood	1
Conditioning	
Myeloablative	10
Reduced intensity	23
GVHD prophylaxis	
CsA plus MTX	25
ATG or CAMPATH	4
CsA plus MMF	4

AML indicates acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndromes; NHL, nonHodgkin lymphoma, HD, Hodgkin disease; MM, multiple myeloma; CR, complete remission; GVHD, graft-versus-host disease; ATG, antithymocyte globulin; CsA, cyclosporine; MMF, mycophenolate motefil; MTX, methotrexate.

The infectious prophylaxis consisted of Trimethoprim-Sulfamethoxazole and Acyclovir.