The Use of Oral Beclomethasone Dipropionate in the Treatment of Gastrointestinal Graft-versus-host Disease: The Experience of the Fukuoka Blood and Marrow Transplantation (BMT) Group

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Abstract

Objective  We examined the therapeutic strategies for treating mild gastrointestinal (GI) graft-versus-host disease (GVHD) using oral beclomethasone dipropionate (BDP) in 15 Japanese patients based on the donor source. The primary objective was to determine the efficacy and toxicity of oral BDP combined with/without low-dose prednisone (PSL).

Methods  Oral BDP was administered with 1 mg/kg/d of PSL in patients undergoing bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT; n=11), and the dose of PSL was tapered off after 22 days. Oral BDP alone was administered in patients undergoing cord blood stem cell transplantation (CBSCT; n=4). The primary endpoint was the rate of treatment success on day 49, as measured according to the improvement or complete resolution of GI symptoms without additional treatment. The secondary endpoints included treatment-related toxicity according to the National Cancer Institute Common Toxicity Criteria version 3.0, the rate of treatment discontinuation due to toxicity, the rate of relapse of acute GVHD by day 100 and the incidence of bacterial, fungal or viral infection, including cytomegalovirus (CMV) antigenemia.

Results  Treatment success was achieved in seven of the 11 (64%) patients undergoing BMT or PBSCT and in all four patients (100%) undergoing CBSCT. Subsequent adverse events included herpes zoster infection, catheter-associated sepsis and CMV enteritis; all affected patients responded well to treatment.

Conclusion  The use of a risk-stratified treatment strategy with oral BDP depending on the stem cell source is effective in patients with mild GI-GVHD.

Key words: beclomethasone dipropionate, graft-versus-host disease, gastrointestinal tract, cord blood stem cell transplantation

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Introduction

Acute graft-versus-host disease (GVHD) remains one of the most severe complications after allogeneic stem cell transplantation (allo-SCT). In particular, gastrointestinal (GI) GVHD amplifies systemic GVHD and induces septicemia by allowing the transmission of intestinal bacteria and their immunostimulatory products into the circulation (1-3). Combined therapy with systemic corticosteroids and prophyllactic calcineurin inhibitors is the standard primary treatment for acute GVHD, including GI-GVHD, and yields a complete response in 30-50% of patients (4, 5). However, the response rates appear to be dependent on the site of GI-GVHD, with inferior responses observed in patients with lower GI-GVHD than in those with upper GI-GVHD or GVHD in other organs (6-10). Considering that long-term systemic immunosuppressive therapy carries a risk of infectious complications, adrenal insufficiency, glucose intolerance and bone demineralization, alternative strategies are required to treat mild GI-GVHD, particularly upper GI-GVHD.

Beclomethasone dipropionate (BDP) is a poorly absorbed topically active corticosteroid whose use may circumvent the adverse effects associated with systemic corticosteroids. As an anti-inflammatory agent, BDP has been shown to be 300-5,000 times more potent than dexamethasone and hydrocortisone (11, 12). Based on encouraging observations in patients with inflammatory bowel disease (13, 14), BDP has been increasingly used to treat GI-GVHD after allo-SCT, with high efficacy (7, 15-19). Prophyllactic effects of oral BDP against early non-infectious pulmonary complications after allo-SCT have also been observed, and the administration of oral BDP can be used to reduce exposure to systemic corticosteroid therapy (6, 20).

Umbilical cord blood is increasingly being used as a donor source for allo-SCT, with a low risk of acute or chronic GVHD, despite the presence of a major disparity in human leukocyte antigens (HLAs) (21-23). A recent study suggested that umbilical cord blood transplantation is significantly associated with a higher probability of improvements following corticosteroid therapy compared with HLAmatched related bone marrow transplantation (24). In the present study, we propose a risk-stratified therapeutic strategy for treating mild GI-GVHD depending on the stem cell source. Based on the hypothesis that GVHD occurring after cord blood stem cell transplantation (CBSCT) is more sensitive to corticosteroids than that occurring after bone marrow transplantation (BMT) or peripheral blood stem cell transplantation (PBSCT), we suggest the use of treatment with BDP alone for CBSC and BDP plus short-term low-dose prednisone (PSL) after BMT and PBSCT. Evidence supporting this strategy is provided by previous reports. For example, Mielcarek et al. showed that initial treatment with low-dose PSL in patients with grade I-II GVHD did not compromise disease control (25), while the addition of oral BDP to a 10-day course of PSL improved the initial treatment effects in patients with grade IIA GI-GVHD (7, 18).

In the present report, we assessed a treatment strategy for mild GI-GVHD using a combination of oral BDP and short-term low-dose PSL based on the donor source.

Materials and Methods

Patient selection

This is a phase II study of BDP therapy combined with low-dose PSL for “Grade IIA GVHD.” The eligibility criteria were as follows: 1) grade IIA GI acute GVHD occurring within 100 days after allogeneic transplantation (with a histologically confirmed diagnosis of upper GI-GVHD), 2) no treatment for GVHD except prophylaxis, 3) the ability to tolerate oral administration, 4) an age of 16-69 years, 5) an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, 6) an adequate main organ function and 7) voluntary written informed consent. The exclusion criteria were as follows: 1) a history of BMT or PBSCT from two or more HLA-mismatched donors, 2) serious main organ dysfunction other than GVHD, 3) a history of serious hypersensitivity to any drug, 4) pregnancy, possible pregnancy or currently lactating and 5) the inability to follow the procedures required in the protocol. “Grade IIA GVHD” was defined as stage I GI-GVHD with stage 0-2 skin manifestations but no liver involvement (26). Biopsy confirmation of GI-GVHD was not required in the patients with lower GI-GVHD if the clinical manifestations were obvious and other differential diagnoses were excluded. As GVHD prophylaxis, the patients received tacrolimus with short-term methotrexate (sMTX), cyclosporine with sMTX or cyclosporine with mycophenolate mofetil (MMF). Cyclosporine was started at a dose of 3 mg/kg/d, and tacrolimus was started at a dose of 0.03 mg/kg/d. The dose of calcineurine inhibitors was adjusted every one to two days in order to maintain the optimum concentration (200-250 ng/mL for cyclosporine, 10-15 ng/mL for tacrolimus). MMF was administered for 30 days after transplantation, with the dose quickly tapered in approximately one week. The main objective was to determine the efficacy and toxicity of oral BDP combined with/without low-dose PSL. We calculated the sample size based on an unacceptable response rate of 0.3 and a desirable response rate of 0.7, with a significance level of 0.05 and a power of 0.90; the required sample size was 15. This study was approved by the Institutional Review Board of each participating institute.

BDP treatment

BDP was administered orally as an emulsion in the patients with upper GI disease and as a pill in the patients with lower GI disease four times a day at a dose of 1.3 mg among those undergoing CBSCT. In addition to BDP, patients undergoing BMT or PBSCT received 1 mg/kg/d of PSL, which was tapered off after 22 days.
Study evaluation

The response was first evaluated three and seven days after treatment initiation. Treatment was abandoned as failed if disease progression was observed on day 3 or if no improvements were observed on day 7. The primary endpoint was the rate of treatment success on day 49. Conditions of this endpoint included no increases in the dose of systemic corticosteroids, additional treatment for systemic GVHD, treatment discontinuation for more than three days due to toxicity or non-relapse mortality. The secondary endpoints included treatment-related toxicity according to the National Cancer Institute Common Toxicity Criteria version 3.0, the rate of treatment discontinuation due to toxicity, the rate of relapse of acute GVHD by day 100 and the incidence of bacterial, fungal and viral infection, including cytomegalovirus (CMV) antigenemia. The responses were evaluated as previously described (16).

Results

Patient characteristics

In total, 16 Japanese patients were treated with oral BDP between October 2008 and December 2010. One patient was excluded from the evaluation due to incomplete data. The patient characteristics are summarized in Table 1. The subjects included eight men and seven women with a median age of 52 years (range, 25-68 years). Allo-SCT was performed in six patients with acute myelogenous leukemia, five patients with acute myelogenous leukemia, one patient with adult T-cell leukemia/lymphoma, one patient with myelodysplastic syndrome and two patients with non-Hodgkin lymphoma. Stem cells were sourced from two HLA-identical family donors, nine unrelated donors and four unrelated cord blood samples. The baseline parameters were similar between the patients who received cord blood and those who did not. Four patients received myeloablative conditioning regimens, and 11 patients received reduced intensity conditioning regimens. GVHD prophylaxis was performed as follows: tacrolimus with sMTX in nine patients, cyclosporine with sMTX in three patients and cyclosporine with MMF in three patients.

Efficacy

The clinical efficacy of BDP treatment is summarized in Table 2. GVHD was observed in the upper GI tract, the lower GI tract and both in six, six and three patients, respectively. Seven of the 15 patients had GVHD of the skin. Treatment with BDP was started on days 19-97 (mean, 36
days) after transplantation and administered for a median of 14 days (range, 3-68 days). Among the 15 patients evaluated in this study, 11 (73%) exhibited treatment success on day 49, as described in the Materials and Methods section. In particular, a CR and PR were achieved in 10 (67%) and one (7%) patient, respectively. Two patients (13%) did not respond to treatment, and two patients (13%) exhibited disease progression. Among the 11 responding patients, relapse was observed in two patients (13%) by day 100. The subsequent administration of a second course of BDP or systemic corticosteroids improved the GI-GVHD in these two patients. All patients treated with CBSCT or myeloablative conditioning responded well, although this finding was not statistically significant. We also found that treatment with BDP tended to be started later in the responders than in the non-responders. No significant differences were observed in the response rates with respect to age, the site of GI-GVHD or the presence of GVHD of the skin (Table 3).

### Toxicity

None of the patients developed adverse reactions to BDP during treatment. However, subsequent adverse events included herpes zoster infection, catheter-associated sepsis and CMV enteritis (Table 2). One patient developed herpes zoster infection that required treatment with acyclovir, and another patient developed catheter-associated sepsis that required treatment with antibiotics. Both patients responded well to their respective treatments. CMV antigenemia was observed in 12 of 15 patients (80%), and three patients (20%) developed CMV enteritis. The treatment of CMV enteritis with antiviral drugs was successful. BDP treatment was not discontinued in any case due to adverse events.

### Discussion

Systemic corticosteroid treatment with 2 mg/kg/d of methylprednisolone is considered the standard first-line treatment for GI-GVHD. However, over the long-term, this treatment is often accompanied by severe treatment-related morbidity (4, 5). In addition, due to relative responsiveness to treatment with immunosuppressive agents, overtreatment remains a hazard in patients with mild GI-GVHD, particularly that of the upper GI tract (6-8). Therefore, the development of new treatment strategies is required to avoid treatment-related morbidity in patients with mild GI-GVHD. The efficacy of oral BDP treatment has become increasingly evident and can be used to reduce systemic corticosteroid exposure in GI-GVHD patients (7, 15-19). In the present study, we assessed the efficacy of a treatment strategy for mild GI-GVHD using a combination of oral BDP and short-term low-dose PSL based on the donor source. Our analysis showed a 73% response rate for grade IIa GI-GVHD, which...
is comparable to the findings of previous reports (16, 18). Considering that a complete response is achieved in only 30-50% of patients treated with systemic corticosteroids, this result indicates that our treatment protocol is a useful alternative to high-dose corticosteroids as an initial therapeutic approach for treating mild GI-GVHD. Of note, all patients receiving PBSCT responded to treatment without requiring systemic corticosteroid therapy, although this observation was not statistically significant (Table 3). Nonetheless, acute GVHD occurring after PBSCT appears more sensitive to corticosteroids than acute GVHD occurring after BMT or PBSCT, as suggested in a recent study (24), supporting the use of an initial treatment strategy for mild GI-GVHD that takes into consideration the donor source. The occurrence of GI-GVHD after PBSCT is also an attractive indication for the use of oral BDP. Interestingly, all patients treated with myeloablative conditioning were responsive to therapy. This result is inconsistent with the findings of previous reports showing that the administration of intensified pretransplant conditioning results in more severe GI-GVHD (3, 27). Moreover, the location of GI-GVHD did not influence the treatment response rate in this study (Table 3). This finding was contrary to our expectations, since previous reports have shown that upper GI-GVHD is more sensitive to treatment than lower GI-GVHD (6). However, the small number of cases is a limitation to our study. Future research using a larger number of cases is required to clarify the influence of donor sources, as well as the pretransplant conditioning intensity and GI-GVHD location, on the efficacy of treatment.

Oral BDP was administered safely, with several mild infectious complications. This is consistent with the results of previous studies reporting that the use of oral BDP does not result in an increased incidence of fungal or bacterial infection after SCT (18, 19), indicating the merits of oral BDP therapy, both alone and in combination with short-term low-dose PSL, as an initial treatment for GI-GVHD. Among infectious complications, CMV enteritis is notable, as the resulting diarrhea is often indistinguishable from the symptoms of GI-GVHD. Conducting endoscopic examinations, along with the appropriate use of anti-CMV agents, is required in cases of suspected CMV enteritis.

In conclusion, our data suggest that the administration of oral BDP after PBSCT or oral BDP plus short-term low-dose PSL after BMT and PBSCT is an effective initial therapeutic approach for treating mild GI-GVHD. The utility of treatment stratification based on the donor source in patients with mild GI-GVHD is worth evaluating in a larger controlled study.

The authors state that they have no Conflict of Interest (COI).

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References

18. McDonald GB, Bourvier M, Hockenbery DM, et al. Oral becl-


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http://www.naika.or.jp/imonline/index.html