A RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF
ORAL BECLOMETHASONE DIPROPIONATE AS A PREDNISONE-SPARING THERAPY
FOR GASTROINTESTINAL GRAFT-VERSUS-HOST DISEASE

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Short title: Oral BDP for intestinal GVHD

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in the preparation of the manuscript; Timothy C. Rodell was the medical director for the trial,
assisted in the analysis, and assisted in the preparation of the manuscript; Ted Gooley performed statistical analyses; Friedrich Schuening entered patients into the trial; Scott D. Rowley entered patients into the trial; Donald David entered patients into the trial; Mark Brunvand, entered patients into the trial; Brian Berryman entered patients into the trial; Sunil Abhyankar entered patients into the trial; Michelle Bouvier collated long-term survival data; George B. McDonald designed the research and co-wrote the manuscript. Note that 9 additional members of the OrBec GVHD Study Group are listed as entering patients into the trial.

**Conflict of Interest Disclosure:** Scott Cruickshank, Timothy C Rodell, and George B McDonald have declared a financial interest in a company whose potential product was studied in the present work. Each of these authors is a consultant to BOR BioPharma, Inc., the sponsor of the study. GBM has an equity position in DOR BioPharma, Inc.
ABSTRACT

We tested the hypothesis that oral beclomethasone dipropionate (BDP) would control gastrointestinal graft-vs-host-disease (anorexia, vomiting, and diarrhea). Patients were randomized to prednisone for ten days and either oral BDP 8 mg/day (N=62) or placebo (N=67) tablets for fifty days. At Study Day-10, prednisone was rapidly tapered while continuing study drug. On an intent-to-treat basis, the risk of GVHD-treatment failure was reduced for the BDP group at Study Day-50 (hazard ratio 0.63, 95% CI 0.35-1.13) and at 30 days follow-up (HR 0.55, 95% CI 0.32, 0.93). Among patients eligible for prednisone taper at Study Day-10, the risk of GVHD-treatment failure was significantly reduced at both Study Days-50 and -80 (HR 0.39 and 0.38, respectively). By day-200 post-transplant, 5 patients randomized to BDP had died, compared to 16 deaths on placebo, a 67% reduction in the hazard of mortality (HR 0.33, p=0.03). In 47 recipients of unrelated and HLA-mismatched stem cells, mortality at transplant day-200 was reduced by 91% in the BDP group, compared to placebo (HR 0.09, p=0.02). The survival benefit was durable to one-year post-randomization. Oral BDP prevents relapses of gastrointestinal GVHD following tapering of prednisone; survival is statistically significantly better among patients receiving BDP.
INTRODUCTION

Gastrointestinal graft-versus-host disease (GVHD) affects up to 60% of patients after allogeneic hematopoietic cell transplant.\(^1\) Intestinal GVHD involves release of cytokines within the mucosa, infiltration of donor T lymphocytes, and crypt cell apoptosis.\(^2,3\) Clinical manifestations include anorexia, nausea, vomiting, diarrhea, and, in patients with severe involvement, fever, cholestasis, protein-losing enteropathy, and sloughing of mucosa.\(^4-8\) In animal studies, the extent of intestinal involvement and T-cell activation in Peyer’s patches are determinants of survival.\(^2,9\) Initial treatment is with prednisone 1-2 mg/kg/day, followed by a prednisone tapering schedule to prevent GVHD relapses and allow recovery of the hypothalamic-pituitary-adrenal axis.\(^4\) Another approach to GVHD treatment involves a 5-day course of prednisolone at 2 mg/kg/day; the response after five days is prognosis-determining.\(^10\) Prednisone-related side effects are common, particularly fatal infections, weakness, hyperglycemia, hypertension, osteopenia, and psychiatric symptoms.

We tested the hypothesis that a topically-active corticosteroid (beclomethasone dipropionate, BDP), taken orally, allows rapid tapering of prednisone while maintaining control of intestinal GVHD. The results show that a 50-day course of treatment with oral BDP reduces the frequency of relapses of GVHD following accelerated withdrawal of prednisone therapy and results in better survival at transplant day-200 and at one year post-randomization, compared to placebo. Because of this survival benefit, we also examined outcomes from a previous randomized trial of a shorter, 30-day course of oral BDP.\(^11\)
METHODS

Patient selection. Patients with symptoms of GVHD were evaluated with endoscopy and mucosal biopsy. If biopsy specimens demonstrated histologic findings of GVHD and stool and mucosal biopsy cultures were negative for pathogens, patients were invited to participate. Patients were excluded if diarrhea exceeded one liter/day, or if skin or liver GVHD were present. All patients received medications for GVHD prophylaxis; patients receiving corticosteroids within 30 days of study entry were excluded. Patients signed informed consent documents approved by the institutional review boards of all participating institutions.

Formulation of BDP. Both immediate release tablets and enteric-coated tablets contained 1 mg of BDP (orBec, DOR BioPharma, Miami FL). The dosing regimen was one immediate-release and one enteric-coated tablet, taken orally four times daily (total daily dose, 8 mg BDP).

Stratification and randomization (Table 1). A blocked stratified allocation scheme was used to balance the treatment groups within study centers. Additional stratifying variables were HLA-matched sibling and use of cutaneous corticosteroids at baseline. Patients were randomized to receive either BDP or identical placebo tablets in a 1:1 allocation.
Table 1. Characteristics of patients according to randomization assignment.

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=67</th>
<th>BDP N=62</th>
<th>Overall N=129</th>
</tr>
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<tbody>
<tr>
<td><strong>Age at randomization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td>44.5 (±13.4)</td>
<td>45.9 (±13.6)</td>
<td>45.2 (±13.5)</td>
</tr>
<tr>
<td>Median</td>
<td>47.0</td>
<td>47.0</td>
<td>47.0</td>
</tr>
<tr>
<td>Range</td>
<td>17-66</td>
<td>6-70</td>
<td>6-70</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>41 61%</td>
<td>36 58%</td>
<td>77 60%</td>
</tr>
<tr>
<td>Female</td>
<td>26 39%</td>
<td>26 42%</td>
<td>52 40%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56 84%</td>
<td>54 87%</td>
<td>110 85%</td>
</tr>
<tr>
<td>American Hispanic</td>
<td>7 10%</td>
<td>4 6%</td>
<td>11 9%</td>
</tr>
<tr>
<td>Asian</td>
<td>1 1%</td>
<td>3 5%</td>
<td>4 3%</td>
</tr>
<tr>
<td>Black</td>
<td>3 4%</td>
<td>1 2%</td>
<td>4 3%</td>
</tr>
<tr>
<td><strong>Days from transplant to randomization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (± SD)</td>
<td>45.7 (± 31.80)</td>
<td>48.3 (± 32.56)</td>
<td>47.0 (± 32.07)</td>
</tr>
<tr>
<td>Median</td>
<td>35.0</td>
<td>37.0</td>
<td>36.0</td>
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<tr>
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<td>18 to 190</td>
<td>18 to 190</td>
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<td><strong>Primary diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Myelogenous Leukemia</td>
<td>22 33%</td>
<td>19 31%</td>
<td>41 32%</td>
</tr>
<tr>
<td>Acute Lymphocytic Leukemia</td>
<td>7 10%</td>
<td>9 14%</td>
<td>16 12%</td>
</tr>
<tr>
<td>Chronic Myelogenous Leukemia</td>
<td>8 12%</td>
<td>8 13%</td>
<td>16 12%</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphoma</td>
<td>7 10%</td>
<td>6 10%</td>
<td>13 10%</td>
</tr>
<tr>
<td>Myelodysplastic Syndrome</td>
<td>6 9%</td>
<td>2 3%</td>
<td>8 6%</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>1 1%</td>
<td>6 10%</td>
<td>7 5%</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>4 6%</td>
<td>2 3%</td>
<td>6 5%</td>
</tr>
<tr>
<td>Chronic Myelomonocytic Leukemia</td>
<td>3 5%</td>
<td>2 3%</td>
<td>5 4%</td>
</tr>
<tr>
<td>Aplastic Anemia</td>
<td>2 3%</td>
<td>1 2%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Hodgkin’s Disease</td>
<td>2 3%</td>
<td>1 2%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>2 3%</td>
<td>1 2%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Acute Promyelocytic Leukemia</td>
<td>0 0%</td>
<td>2 3%</td>
<td>2 2%</td>
</tr>
<tr>
<td>Other*</td>
<td>3 5%</td>
<td>3 5%</td>
<td>6 5%</td>
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<td><strong>Risk of relapse post-transplant</strong></td>
<td></td>
<td></td>
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<tr>
<td>High risk</td>
<td>29 43%</td>
<td>40 65%</td>
<td>69 53%</td>
</tr>
<tr>
<td>Low risk</td>
<td>38 57%</td>
<td>22 35%</td>
<td>60 47%</td>
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<tr>
<td><strong>Source of donor cells</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Peripheral blood stem cells</td>
<td>62 93%</td>
<td>54 87%</td>
<td>116 90%</td>
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<tr>
<td>Bone marrow</td>
<td>5 7%</td>
<td>8 13%</td>
<td>13 10%</td>
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<tr>
<td><strong>Conditioning regimen</strong></td>
<td></td>
<td></td>
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<tr>
<td>Myeloablative</td>
<td>52 78%</td>
<td>36 58%</td>
<td>88 68%</td>
</tr>
<tr>
<td>Non-myeloablative</td>
<td>15 22%</td>
<td>26 42%</td>
<td>41 32%</td>
</tr>
<tr>
<td><strong>Patient/donor relationship</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Patients were considered to be at low risk of relapse following transplant if the indication for transplant was one of these diagnoses: aplastic anemia, chronic lymphocytic leukemia, chronic myelogenous leukemia in chronic phase, chronic myelomonocytic leukemia, acute myelogenous leukemia in first remission, myelodysplastic syndrome, myelofibrosis, myeloproliferative syndrome, and polycythemia vera. Patients with other diagnoses were considered to be at high risk for relapse after transplant.**

**Treatment plan.** Therapy consisted of study drugs plus 10 days of prednisone. The initial 16 patients were administered prednisone 2 mg/kg/day for 10 days; the remaining 113 patients received an initial prednisone dose of 1 mg/kg/day after hypothalamic-pituitary-adrenal axis suppression was observed at the higher dose at the time of Study Day-50 testing. In patients with control of GVHD symptoms at Study Day-10, prednisone was tapered over 7 days (0.25 mg/kg twice daily on Study Days-11 and -12; 0.125 mg/kg twice daily on Study Days-13 and -14; 0.0625 mg/kg twice daily on Study Days-15 and -16), after which patients were maintained on physiologic replacement doses of prednisone (0.0625 mg/kg daily). Patients who did not demonstrate adequate control of GVHD by Study Day-10 were considered treatment failures. Patients received study drug for 50 days, until they met the treatment failure endpoint, or until

<table>
<thead>
<tr>
<th>Related Biological parent</th>
<th>45 67%</th>
<th>43 69%</th>
<th>88 68%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibling</td>
<td>2 3%</td>
<td>0 0%</td>
<td>2 2%</td>
</tr>
<tr>
<td>Other relation</td>
<td>43 64%</td>
<td>40 65%</td>
<td>83 64%</td>
</tr>
<tr>
<td>HLA allele match status in siblings</td>
<td>0 0%</td>
<td>3 4%</td>
<td>3 2%</td>
</tr>
<tr>
<td>Matched</td>
<td>43 64%</td>
<td>39 63%</td>
<td>82 64%</td>
</tr>
<tr>
<td>Mismatched for 1 or more alleles</td>
<td>0 0%</td>
<td>1 2%</td>
<td>1 &lt;1%</td>
</tr>
</tbody>
</table>

*Other primary diagnoses included (one each): biphenotypic acute leukemia, extramedullary leukemia tumor, metastatic renal cell carcinoma, myeloproliferative syndrome, plasmacytic leukemia, and polycythemia vera.*
they were withdrawn from the study. Patients who were declared treatment failures had study drug discontinued; subsequent treatment for GVHD was dictated by their physicians.

**Definitions of treatment failure and efficacy end-points.** Treatment failure was a worsening or recurrence of GVHD that required additional immunosuppressive therapy. The primary efficacy endpoint was the time to treatment failure through Study Day-50. Prospectively defined secondary efficacy endpoints included time to treatment failure 30 days after discontinuation of study drug and survival at day-200 post-transplant. Survival at one year post-randomization was evaluated in a retrospective manner.

**Evaluation of drug safety and adverse events.** Safety assessment was based on cumulative prednisone exposure, the incidence and degree of hypothalamic-pituitary-adrenal axis suppression, and rates of adverse events.

**Statistical methods.** A total sample size of approximately 130 patients (65 in each group) with 48 treatment failure events was determined to provide 80% power for a comparison of time-to-treatment-failure between treatment groups using the log-rank test. The sample size calculation was based on a two-sided significance level of 0.05 and assumed treatment failure rates at Study Day-50 of 0.30 and 0.55 for the BDP and placebo groups, respectively. These assumptions were predicated upon the results of a previous randomized trial of BDP in the same patient population. The study was planned to enroll approximately 130 patients to compensate for loss to follow-up for the secondary endpoints and to provide adequate safety data. Analysis of the time-to-treatment-failure and survival endpoints includes all randomized patients. The primary analysis of time-to-treatment-failure and survival post-randomization was based on the Kaplan-Meier method and log-rank test, stratified by donor type (HLA-matched sibling vs. unrelated or HLA-mismatched donor). For each endpoint, the hazard ratio for treatment was estimated based
on a stratified Cox proportional hazards model that included a term for treatment group. Because of the variable length of time among patients between transplant and randomization, randomization to BDP treatment was defined in the proportional hazards model as a time-dependent covariate for the day-200 post-transplant survival endpoint. Under this model, the comparison between BDP and placebo was made using the Wald chi-square test. For the primary analysis, the time-to-treatment-failure was right-censored for patients who discontinued study drug during the first 50 days without meeting the criteria for treatment failure, provided the reason for discontinuation was not related to uncontrolled GVHD or study drug-related toxicity. This determination was made in real time and prior to analysis by the study’s medical monitor who was blinded to the patients’ randomly assigned treatment. For each survival endpoint, a variety of multivariate models was used to determine if the reduced mortality risk attributed to BDP in the univariate model was still present after accounting for subject-, disease-, and transplant-related factors. Hypothesis tests of the primary and secondary endpoints were performed using a two-sided significance level of 0.05. No adjustments were made to the significance level for inferential tests of the secondary endpoints. All patients who received at least one dose of BDP or placebo were included in the assessment of safety. In addition to the primary analysis of the treatment failure and survival endpoints, an exploratory analysis was performed to assess the impact of the 12 patients who experienced treatment failure shortly after randomization (i.e., during the first 10 days of protocol treatment during which oral BDP is unlikely to affect initial responses to concomitant high-dose corticosteroids). Patients who experienced treatment failure during this period were right-censored at the time of early treatment failure. Analyses were done using SAS® (version 8.2), R (version 2.0.1), and S-Plus (version 6.2) software.
RESULTS

Patient demographics (Table 1). Between July 2001 and July 2004, 129 patients were enrolled. With the exception of the transplant conditioning regimen (myeloablative or non-myeloablative), no major imbalances were noted between the treatment groups for baseline transplant-related characteristics. The percentage of patients who received a non-myeloablative conditioning regimen was approximately two-fold higher in the BDP group compared to placebo (Table 1).

Analysis of treatment efficacy (Figure 1). By Study Day-50, there were 30 GVHD-treatment failures in the placebo group and 18 in the BDP group. Fourteen patients (7 in each group) discontinued from study drug early for reasons not related to uncontrolled GVHD or study drug-related toxicity and were right-censored on the day of their last dose of study drug. The cumulative rate of GVHD-treatment failure was 31% for BDP vs. 48% for placebo; the hazard of treatment failure was reduced in the BDP group relative to placebo, although not statistically significantly so (HR 0.63; 95% CI: 0.35, 1.13; p=0.12 stratified log-rank test) (Figure 1A).
Figure 1. Time to GVHD-treatment failure through Study Day-80 with hazard ratios and confidence intervals. Panel A shows product limit estimates on an intent-to-treat basis; panel B shows estimates with a guarantee period for the first ten days of treatment. Estimates are based on the Kaplan-Meier method. The hazard ratios at Study Day-50 were A) 0.63; 95% CI: 0.35, 1.13; p=0.12 and B) 0.39; 95% CI: 0.19, 0.81; p=0.009, respectively.
The majority of patients with GVHD treatment failure had recurrent gastrointestinal symptoms; three patients had gastrointestinal and skin GVHD; six had skin GVHD; two had liver GVHD; and one had bronchiolitis obliterans-organizing pneumonia. GVHD-treatment failure occurred during the first 10 days of prednisone treatment in twelve of the 48 patients with GVHD-treatment failure by Study Day-50 (8 BDP, 4 placebo). The impact of early treatment failures on the primary endpoint was assessed by designating the first 10 days of treatment as a guarantee period (see Methods). Patients with treatment failure during the guarantee period were right-censored on the day of GVHD-treatment failure. For this analysis, the risk of GVHD-treatment failure by Study Day-50 was statistically significantly reduced for the BDP group relative to placebo (hazard ratio 0.39; 95% CI: 0.19, 0.81; p=0.009 stratified log-rank test) (Figure 1B).

By Study Day-80, 30 days after discontinuation of study drug, a total of 22 patients in the BDP group and 39 patients in the placebo group were GVHD-treatment failures. Six patients (4 BDP, 2 placebo) withdrew from study during the 30-day post-treatment observation period who did not experience treatment failure prior to their withdrawal. Based on blinded review, the reason for withdrawal was classified as unrelated to uncontrolled GVHD or study drug-related toxicities. The time to treatment failure was right-censored for the 6 patients on the day of their last study visit. The cumulative treatment failure rates were 39% for BDP and 65% for placebo. For the entire 80-day study period, the risk of treatment failure was statistically significantly reduced for patients in the BDP group relative to placebo (hazard ratio 0.55; 95% CI: 0.32, 0.93; p=0.02, stratified log-rank test) (Figure 1A). In an analysis using a 10-day guarantee period, the risk of treatment failure was statistically significantly reduced for the BDP arm relative to
placebo for the 80-day study period (hazard ratio 0.37; 95% CI: 0.20, 0.69; p=0.001, stratified log-rank test) (Figure 1B).

Survival analysis at transplant day-200 (Table 2). By day-200 post-transplant, 5 patients (8%) who had been randomized to BDP had died, compared to 16 deaths (24%) among patients who had been randomized to placebo. Based on a stratified time-dependent Cox proportional hazards model, the risk of mortality during the 200-day post-transplant period was 67% lower with BDP treatment compared to placebo treatment (hazard ratio 0.33; 95% CI: 0.12, 0.89; p=0.03, Wald chi-square test). The number of deaths (21) does not allow the inclusion into the regression model of more than 1 or 2 variables in addition to the treatment group variable. The only factor that was largely imbalanced between the treatment groups was the planned intensity of the transplant conditioning regimen (Table 1). Adjustment for this factor did not, however, alter the estimated hazard ratio for mortality for BPD treatment vs. placebo (adjusted hazard ratio 0.33, 95% CI: 0.12, 0.91; p=0.03, Wald chi-square test). Moreover, the estimated treatment effect also remained generally unchanged after adjusting for various combinations of other factors (resulting in models with no more than 2 factors in addition to treatment group), including study center, patient age and gender, primary diagnosis (high relapse risk or not), source of donor cells (marrow, peripheral blood stem cells), and donor-recipient HLA match (data not shown).

The most common proximate causes of death by transplant day-200 were relapse of the underlying malignancy and infection (Table 2). Relapse of the hematologic malignancy had contributed to the deaths of 9/67 patients (13.4%) in the placebo arm and 3/62 patients (4.8%) in the BDP arm. Infection contributed to the deaths of 9/67 patients (13.4%) in the placebo arm and 3/62 (4.8%) in the BDP arm. Acute or chronic GVHD was the proximate cause of death in 3/67 patients (4.5%) in the placebo arm and in 1/62 (1.6%) in the BDP arm.
Table 2. Analysis of survival at transplant day-200 among patients in the current trial and in the previous randomized, placebo-controlled trial of oral BDP.

<table>
<thead>
<tr>
<th></th>
<th>Current trial</th>
<th>Previous trial 11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>BDP</td>
</tr>
<tr>
<td>Number randomized</td>
<td>67</td>
<td>62</td>
</tr>
<tr>
<td>Number (%) who died</td>
<td>16 (24%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Hazard ratio (95% confidence interval)</td>
<td>0.33 (0.12, 0.89)</td>
<td>0.47 (0.12, 1.87)</td>
</tr>
<tr>
<td>Death with infection*</td>
<td>9 (13%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Death with relapse*</td>
<td>9 (13%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

*Some patients died with both infection and relapse of their underlying malignancy.

There was a statistically significant interaction (p=0.05) between donor type (HLA-matched sibling vs. other donors) and use of BDP for the outcome day-200 mortality, suggesting the need for separate analyses according to donor type. Among 47 patients who had received stem cells from unrelated or HLA-mismatched donors, 1 of 23 patients (4%) who had been randomized to BDP had died, compared to 10 deaths (42%) among 24 patients who had been randomized to placebo, leading to a statistically significantly reduced risk of day-200 mortality (hazard ratio 0.09; 95% CI: 0.01, 0.70; p=0.02, Wald chi-square test). On the other hand, among 82 patients who had received stem cells from an HLA-matched sibling, 4 of 39 (10%) patients randomized to BDP had died by day 200, compared to 6 of 43 (14%) deaths among patients randomized to placebo, leading to a lower risk of mortality, but not statistically significantly so (hazard ratio 0.83; 95% CI: 0.23, 2.93; p=0.77, Wald chi-square test).
**Survival analysis at one year after randomization (Figure 2A).** Of 129 patients randomized, two were lost to follow-up within one year of randomization (last contacted at 321 and 354 days post-randomization; both patients had been randomized to BDP); in the survival analysis these patients were right censored on the date of last contact. All other surviving patients were followed a minimum of one year after randomization. Overall, 28 patients (42%) in the placebo group and 18 patients (29%) in the BDP group died within one year of randomization (hazard ratio 0.54, 95% CI: 0.30, 0.99, p=0.04, stratified log-rank test) (Figure 2A).
Figure 2. Survival of patients to one year after randomization to either BDP or placebo. 
A) The current patient cohort (N=129); B) Patients from the previous randomized trial (N=60)\textsuperscript{11}. 

A) 

\begin{itemize}
  \item HR = 0.54 (95\% CI: 0.30, 0.99)
  \item p = 0.04
\end{itemize}

B) 

\begin{itemize}
  \item HR = 0.55 (95\% CI: 0.20, 1.56)
  \item p = 0.26
\end{itemize}
Safety and adverse events. The frequencies of severe adverse events, adverse events related to study drug, and adverse events resulting in study drug discontinuation were all higher in the placebo group. Patients who remained on BDP until Study Day-50 had a higher likelihood of having biochemical evidence of abnormal HPA function compared to patients on placebo.

Survival analysis of patients in a previous randomized trial of oral BDP. This trial enrolled 60 patients, 31 randomized to oral BDP and 29 to placebo. The duration of treatment with study drug was 30 days, with a ten-day follow-up period. The treatment response rate at Study Day-30 was 71% for BDP vs. 41% for placebo (p=0.02). Analysis of survival at day-200 post-transplant is shown in Table 2. Three patients (10%) who had been randomized to BDP had died, compared to 6 deaths (21%) among patients who had been randomized to placebo, leading to a reduced hazard of day-200 mortality, although not statistically significantly different. By transplant day-200, relapse of hematologic malignancy had contributed to the deaths of 4/29 patients (14%) in the placebo arm and 1/31 patients (3%) in the BDP arm. Infection contributed to the deaths of 5/29 patients (17%) in the placebo arm and 2/31 (6%) in the BDP arm. By one year after randomization, 9 of 29 patients in the placebo group and 6 of 31 patients in the BDP group had died (Figure 2B).

Long-term survival. As of September 1, 2005, median follow-up of patients in the two randomized trials of BDP was 3.5 and 3.6 years for patients in placebo and BDP groups, respectively, with an overall range of 10.6 months to 11.1 years. The risk of mortality was 37% lower for patients randomized to BDP compared to placebo (hazard ratio 0.63, p=0.03, stratified log-rank test).
**DISCUSSION**

This placebo-controlled trial demonstrates that oral BDP allows prednisone to be rapidly tapered with fewer recurrences of GVHD. Although the endpoint time-to-treatment failure by Study Day-50 did not reach statistical significance, the outcome of all clinically-important secondary endpoints, including Study Day-80 efficacy, day-200 survival, and survival at one year after randomization) were statistically significantly better in the BDP group. These results confirm those of a smaller, single-center, placebo-controlled trial of BDP. In patients who had been randomized to BDP in the current trial, there were reductions in the hazard of mortality of 66% and 46% at day-200 and at one year after randomization, respectively. The earlier, sixty-patient randomized trial showed similar reductions in the hazard of mortality. The current trial was undertaken to extend BDP treatment from 30 days to 50 days and to demonstrate efficacy in centers with disparate practices. In an analysis of patients in the current study who had received cells from unrelated or HLA-mismatched donors, the reduction in the hazard of mortality at day-200 was 91% among patients randomized to BDP, compared to placebo. Patients with abdominal pain, secretory diarrhea in excess of one liter daily, intestinal bleeding, or liver and skin GVHD were not included in this study, as patients who were more likely to develop severe GVHD were not optimal candidates for a strategy that attempted to minimize prednisone exposure.

The patients enrolled are representative of most patients now presenting with acute GVHD, as more severe GVHD has become less common than in the past. The beneficial effects of topical corticosteroids for mucosal inflammatory diseases of the intestinal tract, lungs, and nasopharynx have been known for over 30 years. Exacerbations of asthma, chronic obstructive pulmonary disease, and Crohn’s disease respond to high-dose prednisone therapy, but maintenance therapy is often accomplished with topical...
corticosteroids.28,29 Because GVHD involves the mucosa from the stomach to the rectum, formulations of oral BDP were composed of an immediate-release tablet, bioavailable to gastric, duodenal, and jejunal mucosa, and an enteric-coated tablet, for jejunal, ileal, and colonic mucosa.30,31 Oral BDP is biologically active as an immunosuppressive drug in vivo; the parent compound is metabolized in intestinal mucosa and the liver to beclomethasone-17-monopropionate (17-BMP), which has ~25-fold greater glucocorticoid receptor binding activity than BDP.33 BDP does not appear in the systemic circulation because of its metabolism in intestinal mucosa and the liver, but 17-BMP can be detected in the blood stream.34 It is believed that the primary anti-inflammatory effect of oral BDP occurs in the gastrointestinal mucosa as both BDP and 17-BMP are present in high concentrations there. Compared to prolonged prednisone exposure to control GVHD, any systemic effect of BMP in predisposing patients to infection must be relatively minor, as patients randomized to BDP had infrequent fatal infections and better day-200 post-transplant survival.

A treatment that controls the signs and symptoms of GVHD while avoiding prolonged systemic immunosuppression is likely to result in fewer serious infections. High-dose glucocorticoids decrease immune responses to CMV and increase the risk of uncontrolled CMV viremia during antiviral therapy; increase the risk of invasive aspergillosis and mold infection-related death after HCT with non-myeloablative conditioning regimens and greatly increase the risk of blood stream infections following reduced intensity cord blood transplants.39 We speculate that the frequency of leukemic relapse may be higher in the placebo arm because protracted exposure to prednisone to control symptoms of GVHD abrogates T-cell responses; however, the study was not designed to address this question.
Other potential mechanisms by which a highly potent topical corticosteroid might improve outcomes are blunting of inflammatory cytokine production by T cells in intestinal mucosa, inhibition of T cell-mediated apoptosis of epithelial cells, induction of apoptosis in activated effector T cells, and deviation of T cells responses toward tolerance or non-responsiveness. Several studies have shown that glucocorticoids inhibit the differentiation and maturation of dendritic cells in vitro. These effects might help to preserve integrity of the mucosal surface, thereby reducing activation of innate immune mechanisms.

With the exception of adrenal axis suppression, we could not identify adverse reactions to oral BDP in the current study, or in prior studies that specifically examined infection as an adverse event. The use of BDP inhalers has been associated with oropharyngeal and esophageal candidiasis, but oral delivery of BDP did not result in an increased incidence of fungal or bacterial colonization or infections after hematopoietic cell transplant. Metabolites of BDP are systemically bioavailable, resulting in decreased adrenal responsiveness over time of drug exposure. Two recent studies of long-term use of oral, topically-active corticosteroids in doses similar to those used in this trial demonstrated little evidence of clinical adrenal insufficiency.

Two randomized trials have shown that oral BDP prevents relapses of acute gastrointestinal GVHD after accelerated withdrawal of prednisone therapy. The effect is durable even following discontinuation of BDP. We hypothesize that topical therapy with BDP improved survival by limiting GVHD-related gastrointestinal epithelial injury, preserving the mucosal barrier, reducing the need for systemic glucocorticoid treatment, and reducing the frequency of life-threatening infections. The duration of the survival benefit in patients randomized to BDP, however, will require longer follow-up.
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A randomized, placebo-controlled trial of oral beclomethasone dipropionate as a prednisone-sparing therapy for gastrointestinal graft-versus-host disease

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