

A High-Dose Pulse Steroid Regimen for Controlling Active Chronic Graft-Versus-Host Disease

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Received March 8, 2001; accepted July 30, 2001

ABSTRACT

Corticosteroids remain essential for controlling active chronic graft-versus-host disease (cGVHD). However, the optimum dose and administration schedule is unknown. We have reviewed our results in 61 patients with severe refractory cGVHD who were treated with a high-dose pulse steroid regimen (PS) consisting of methylprednisolone at 10 mg/kg per day for 4 consecutive days, with subsequent tapering doses. After 4 days, all patients received a course of additional immunosuppressive therapy. The median age of the 56 patients who were evaluable for response was 32 years (range, 0.2-57 years). Patients had failed a median of 2 (range, 1-5) treatments prior to the PS. The median follow-up for 45 surviving patients after PS was 1.5 years. The probability of survival at 1 year and 2 years after PS was 88% (95% confidence interval [CI], 76%-95%) and 81% (95% CI, 65%-91%), respectively. Twenty-seven patients (48%) showed a major response to PS with substantial improvement of cGVHD manifestations, including softening of the skin, increased range of motion, and improved performance status; 15 patients (27%) showed a minor response, defined as improvement in some but not all symptoms of cGVHD. Of the 42 responders, 21 (50%) had progression of their cGVHD afterwards. The median time to progression was 1.9 years. The probability of progression at 1 and 2 years after PS was 36% (95% CI, 23%-53%) and 54% (95% CI, 38%-71%), respectively. The probability of progression at 1 year was 25% (95% CI, 12%-47%) and 55% (95% CI, 32%-81%) for patients who had major and minor response, respectively (hazard ratio, 2.13). Ten of the 42 responders (24%) were able to discontinue all systemic immunosuppressive treatments. The probability of discontinuation at 1 and 2 years after PS was 9% (95% CI, 3%-25%) and 27% (95% CI, 15%-48%), respectively. The treatment was well tolerated with no serious adverse events. Our results suggest that PS is a well-tolerated regimen for achieving rapid clinical response in the majority of patients with cGVHD who failed on multiple previous therapies. Further studies are warranted to maintain the efficacy of this regimen by combining with new active agents in cGVHD.

KEY WORDS:

Chronic • Graft-versus-host disease • GVHD • Steroid treatment

INTRODUCTION

Although chronic graft-versus-host disease (cGVHD) has a beneficial graft-versus-leukemia effect, it also has a detrimental effect on the long-term outcome and quality of life following allogeneic blood and marrow transplantation (BMT). Despite efforts to decrease the incidence and severity of acute GVHD, cGVHD has emerged as an increasingly frequent complication of BMT, due to increased use of mismatched and unrelated donors [1] and, recently, the

use of allogeneic peripheral blood as a source of hematopoietic stem cells [2-4].

Our recent data on 151 patients showed that the median cGVHD-specific survival was 11.4 years after the diagnosis of cGVHD [5]. However, the probability of long-term survival in patients with poor prognostic features, such as extensive (>50%) skin involvement, thrombocytopenia (<100 K/mm³), poor performance status (Karnofsky performance score <50%), and progressive type of onset, was <20% once they failed primary therapy [5]. Although a variety of new drugs have come to the market and are currently being tested, only minor progress has been made in the treatment of progressive or refractory cGVHD. Once

Presented at the 2001 ASBMT Meeting in Keystone, Colorado.

Table 1. Patient Characteristics (N = 56)*

	n (%)
Median age 32 y (range, 0.2-57 y)	
Male/female	33/23 (59/41)
Underlying diseases	
Chronic myelogenous leukemia	17 (29)
Acute myeloid leukemia	15 (27)
Acute lymphoblastic leukemia	6 (10)
Aplastic anemia	5 (9)
Multiple myeloma	4 (7)
Non-Hodgkin's lymphoma	2 (4)
Myelodysplastic syndrome	2 (4)
Paroxysmal nocturnal hemoglobinuria	1 (2)
Thalassemia	1 (2)
Fanconi anemia	1 (2)
Myelofibrosis	1 (2)
Chronic granulomatous disease	1 (2)
Donor type	
HLA-identical, related	40 (72)
HLA-identical, unrelated	12 (21)
One antigen mismatch	4 (7)
Source of graft	
Bone marrow	52 (93)
Blood	4 (7)
Transplantation date	
1988-1993	28 (50)
1994-1999	28 (50)
GVHD prophylaxis	35†
Cyclosporine alone	16 (46)
Cyclosporine + methotrexate ± ATG	7 (20)
Cyclosporine + methotrexate + prednisone ± ATG	4 (11)
Cyclosporine + prednisone	4 (11)
T-cell depletion	1 (3)
Others	3 (9)

*GVHD indicates graft-versus-host disease; ATG, antithymocyte globulin.

†Denominator indicates number of patients for whom data were present.

cGVHD has progressed after the initial therapies of cyclosporine and prednisone [6], the strategy of subsequent treatment is not well established.

Corticosteroids with or without other immunosuppressive agents such as FK-506 (tacrolimus) [7] or cyclosporine [6] still remain the mainstay of therapy for cGVHD. However, the optimum dose, administration schedule, and type of corticosteroid treatment for controlling the acute progression of GVHD are unknown. Although several reports compare 10 mg/kg per day with lower doses of glucocorticoids in the up-front treatment of acute GVHD [8-10], no consensus has been reached about the optimum high-dose glucocorticoid regimen in GVHD. There are also no data about the role of a high-dose corticosteroid regimen in the treatment of cGVHD. The utility of pulses of steroids in cGVHD has not been reported.

In rheumatology and clinical immunology, acute flares or particularly severe forms of rheumatic diseases, such as systemic lupus erythematosus, vasculitis, polymyositis, and rheumatoid arthritis, are examples of the successful use of high-dose glucocorticoid therapy, usually 10 to 15 mg/kg per day times 3 days. Pulse therapy results in termination

of the exacerbation or regression of a severe form of disease in a high proportion of cases, with a relatively low incidence of side effects.

The following high-dose pulse steroid (PS) regimen that we describe has always been a standard approach in controlling severe refractory cGVHD at Johns Hopkins. This report summarizes our experience with this PS regimen in cGVHD. It examines the question of whether response to PS is predictive of response to future therapy, ability to control cGVHD leading to discontinuation of all immunosuppressive treatments, and survival.

PATIENTS AND METHODS

Patients

Between February 1988 and June 1999, 61 patients with clinicopathologic diagnosis of active cGVHD refractory to previous systemic immunosuppressive therapies were treated with a PS regimen followed by an immunosuppressive therapy protocol that was active in our institution at that time. The majority of patients were referred from other centers to our GVHD clinic for the management plan. Patient characteristics are summarized in Table 1. Five patients who were lost to follow-up after receiving PS therapy were not included in the analyses. The median age of 56 patients who were evaluable for response was 32 years (range, 0.2-57 years). Stem cell donors were HLA-identical siblings in 40 patients (72%), HLA-identical unrelated donors in 12 patients (21%), and 1-antigen mismatched sibling donor in 4 patients (7%). The source of stem cell was bone marrow in 52 patients (93%) and blood in 4 patients (7%). One patient received a nonmyeloablative HLA-identical bone marrow transplant. The clinical diagnosis of cGVHD had to be confirmed by clinical findings and histopathology of the skin in all patients and, if indicated, liver or mucous membrane biopsies before the PS therapy. Other cGVHD-related features are shown in Table 2.

PS Treatment Regimen

Step 1 (Days 1 Through 4). Patients diagnosed as having cGVHD, either flared after responding to a course of immunosuppressive therapy or progressed while on therapy, received PS treatment consisting of high-dose pulse methylprednisolone at 10 mg/kg per day given either orally or intravenously for 4 consecutive days (Figure 1). All dosing was based on actual body weight.

Step 2 (Day 5 and Onward). Patients completing a 4-day high-dose PS regimen were started on a new systemic immunosuppressive therapy, which was decided by the institutional protocol active at that time (Table 3). Patients who were receiving a corticosteroid prior to the PS therapy were restarted on the same dose of steroid they were previously on and gradually tapered off over 4 weeks. Mostly, the PS treatment was administered under the supervision of patients' local oncologists in their hometowns. All adverse effects occurring during the PS administration and within the 1-month period following the treatment were retrieved.

For patients showing improvement, the new immunosuppressive regimen was continued according to the protocol or until cGVHD progression. Patients who had no response to PS plus their new immunosuppressive regimen

Table 2. Characteristics of cGVHD at Diagnosis*

	n (%)
Type of cGVHD	55†
Progressive	12 (22)
Quiescent	20 (36)
De novo	23 (42)
Histology of cGVHD	54†
Lichenoid	22 (41)
Sclerodermatous ± lichenoid	32 (59)
Biopsy sites for cGVHD diagnosis‡	37†
Skin	30 (70)
Oral cavity	9 (21)
Liver	4 (8)
Extent of skin involvement	49†
No skin involvement	6 (12)
≤50% body surface area	14 (29)
>50% body surface area	29 (59)
Number of risk factors at diagnosis§	49†
None	16 (33)
1 or 2	31 (63)
3	2 (4)

*cGVHD indicates chronic graft-versus-host disease.

†Denominator indicates number of patients for whom data were present.

‡Six patients had >1 biopsy site.

§Risk factors at diagnosis [5]: extensive skin involvement (>50%), platelets ≤100,000/μL, and progressive-type onset.

after 3 months of therapy and those who subsequently progressed after the initial response to PS were treated with another salvage regimen during their follow-up. PS was not repeated in patients who failed on the initial attempt.

Study Definitions

Response. Response was evaluated based on the changes in signs and symptoms of skin, joint, liver, mouth, eye, and other cGVHD involvement by clinical criteria. Each organ was evaluated for response an overall response was determined. The following definitions of response were used.

Major response: Complete resolution or unequivocal improvement in all of the cGVHD signs and symptoms after PS while on immunosuppressive therapy. Signs and symptoms were measured against scores obtained at baseline evaluation. Patients had to show improvement in 1 or more systems scores and have no signs of flare in others.

Minor response: Improvement in some disease signs and symptoms but progression or no change in others while on immunosuppressive therapy. Patients had to show improvement in 1 or more organ systems while worsening (flare) or having no change in others.

No response: Increase or no improvement in any disease signs or symptoms despite immunosuppressive therapy. Patients had to have flare in 1 or more organ systems without a response in any other. Failure to improve in any manifestation of cGVHD was also considered as failure to

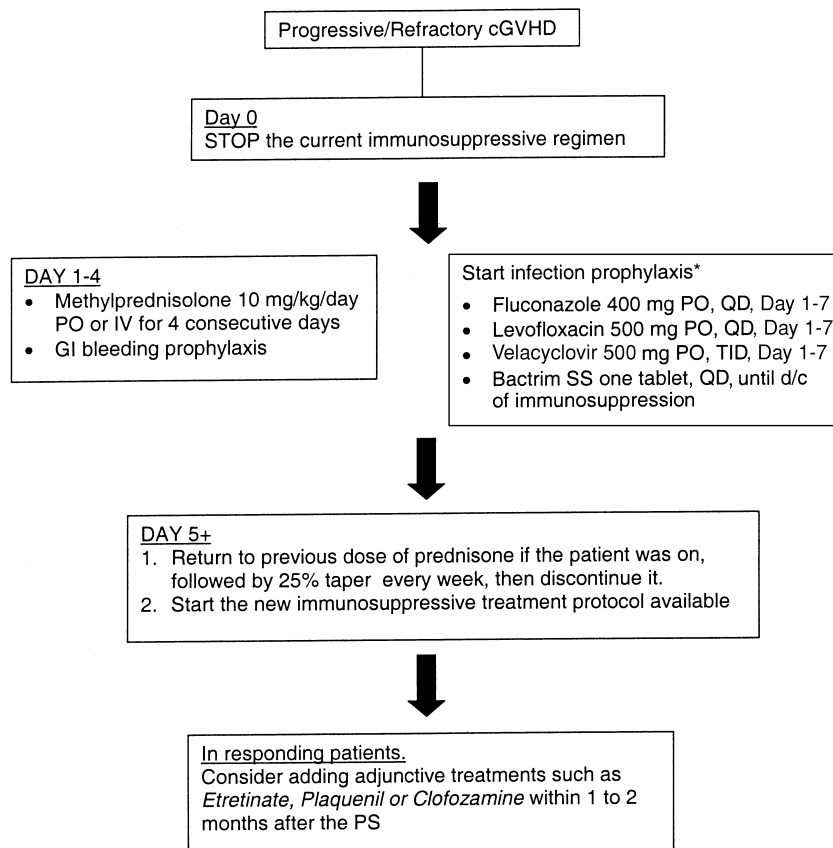


Figure 1. High-dose pulse methylprednisolone (PS) regimen used at Johns Hopkins. cGVHD indicates chronic graft-versus-host disease; PO, by mouth; IV, intravenous; GI, gastrointestinal; d/c, discontinuation; QD, every day; TID, 3 times a day; PS, high-dose pulse steroid regimen.

*Current infectious prophylaxis used for patients with cGVHD.

Table 3. Immunosuppressive Regimens Used in the Treatment of cGVHD (N = 56)*

Regimen	n (%)
Initial treatment for cGVHD at diagnosis	
Prednisone only	7 (12)
Cyclosporine + prednisone ± PUVA	32 (57)
FK-506 + prednisone	5 (9)
FK-506 + MMF	2 (4)
Cyclosporine + prednisone + azathioprine	5 (9)
Cyclosporine + prednisone + thalidomide ± PUVA	1 (2)
Others	4 (7)
Treatment immediately prior to PS	
Prednisone only	6 (11)
Adjunctive therapy only†	7 (13)
Cyclosporine + prednisone ± adjunctive therapy	12 (22)
Cyclosporine + prednisone + thalidomide ± adjunctive therapy	4 (7)
Cyclosporine + prednisone + azathioprine ± adjunctive therapy	4 (7)
FK-506 + MMF + prednisone	14 (25)
Photopheresis	3 (5)
Others	5 (9)
Unidentified	1 (2)
Treatment following PS	
FK-506 + MMF + steroid (taper) ± etretinate	20 (36)
FK-506 + steroid ± etretinate	8 (14)
Cyclosporine + prednisone + etretinate	14 (25)
Cyclosporine + prednisone + thalidomide	6 (11)
Pentostatin + steroid (taper)	3 (5)
Others	5 (9)

*cGVHD indicates chronic graft-versus-host disease; PUVA, psoralen and ultraviolet A light; MMF, mycophenolate mofetil; PS, high-dose pulse steroid regimen.

†Adjunctive therapies included topical corticosteroids, PUVA, etretinate, clofazamine, and plaquenil.

respond, even when there was no worsening of the symptoms and signs of cGVHD.

Progression. Progression of cGVHD was defined as clinically worsening, active cGVHD compared with the signs and symptoms of cGVHD at the beginning of PS therapy. The clinical criteria for progression were stopping the immunosuppressive regimen that was started immediately after PS and instituting another regimen in full dose to control the cGVHD progression.

Statistical Analysis

The major statistical end points of this study were response, time to progression, and time to discontinuation of all systemic immunosuppressive therapies after PS. For categorical predictors, response rates were compared using chi-square tests or Fisher exact tests when data were sparse. Continuous predictive factors were tested using logistic regression. Event times were measured in years from the first day of PS therapy to time of cGVHD progression, discontinuation of all systemic immunosuppressive treatment, death, and/or last follow-up. Survival was defined as the time until death or last follow-up. The overall survival analysis included all patients. Only patients who were considered responders were included in the time to progression

and discontinuation of immunosuppression analyses and figures. Time to progression was defined as the time until cGVHD progression or last follow-up. Deaths without progression were censored using the longest follow-up time for the time to progression analysis and showed separately as a competing risk. Time to discontinuation of all treatment was defined as the time from the PS treatment until the date of discontinuation of all systemic immunosuppressive therapies. Deaths without discontinuation were censored using the longest follow-up time for the time to discontinuation analysis and showed separately as a competing risk. The death as a competing risk analyses exclude deaths after progression or discontinuation of immunosuppression. The probabilities of survival, progression, and discontinuation of all systemic immunosuppressive therapies were estimated using the Kaplan-Meier method [11]. Point estimates are given ±95% confidence bounds [12]. The data were analyzed as of June 29, 2001, using STATA 6.0.

RESULTS

Of 61 patients, 56 were evaluable for response. Five patients who received PS treatment were lost to follow-up and therefore not included in analysis. Patients were started on PS therapy after failing a median of 2 treatment regimens/courses (range, 1-5 courses) given over a median of 12.5 months (range, 2-94 months) after the initial diagnosis of cGVHD. Patients received a median of 11 months (range, 1-94 months) of systemic corticosteroid with or without other immunosuppressive agents prior to PS (Tables 3 and 4). The median dosage of prednisone that patients were taking at the time of PS was 0.2 mg/kg per day (range, 0-2.5 mg/kg per day) (Table 4). Fifty-four patients (96%) received PS mainly because of severe cutaneous cGVHD. One patient had progressive liver and oral cGVHD and another had bronchiolitis obliterans.

Table 4. Previous Treatment of cGVHD*

Number of treatment regimens prior to PS, n (%)	n = 54†
1	11 (22)
2	17 (31)
3	14 (25)
4	9 (16)
5	3 (6)
Total duration of previous treatments, mo	n = 49†
Median (range)	12.5 (2-94)
Total duration of previous steroid treatment, mo	n = 49†
Median (range)	11 (1-94)
Dosage (mg/kg per day) of prednisone immediately prior to PS, n (%)	n = 49†
0	12 (25)
0-0.5	26 (53)
0.5-1.0	5 (10)
1.0-1.5	4 (8)
>1.5	2 (4)
Median (range), mg/kg per day	0.2 (0-2.5)

*cGVHD indicates chronic graft-versus-host disease; PS, high-dose pulse steroid regimen.

†Denominator indicates number of patients for whom data were present.

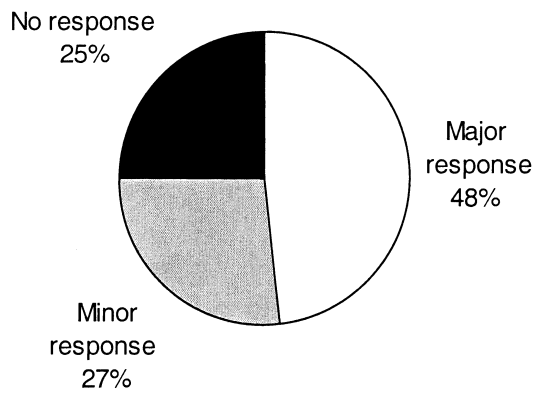


Figure 2. Response to high-dose pulse steroid regimen in 56 patients.

Response to Therapy

Overall, 42 patients (75%) were classified as responders and 14 (25%) as nonresponders, as shown in Figure 2. Twenty-seven patients (48%) showed a major response to PS with substantial resolution of all cGVHD manifestations, including softening of the skin, increased range of motion, and improved performance status. Fifteen patients (27%) showed a minor response. Univariate analysis did not identify any clinical parameter predictive of response. There was no difference in achieving response between the 2 groups of patients (70% and 83%) who were and were not on corticosteroids just before PS therapy. The proportion of nonresponders/responders was also not different by age, sex, donor type, stem cell source, type of onset of cGVHD, and duration of prior cGVHD treatments including corticosteroids. In addition, we could not find a statistically significant correlation between the dose of corticosteroid that patients received prior to the PS and response. The patient with bronchiolitis obliterans did not respond to PS.

Survival

As of June 29, 2001, 45 of the 56 patients are alive with a median follow-up of 1.5 years. The probability of survival

at 1 year and 2 years after PS was 88% (95% confidence interval [CI], 76%-95%) and 81% (95% CI, 65%-91%), respectively (Figure 3).

Time to Failure (Progression of cGVHD)

Of the 42 responders, 21 (50%) had subsequent progression of their cGVHD. Six responders (14%) died without having documented progression. The main causes of death in these patients were late infections complicated by multiorgan failure ($n = 4$), pulmonary emboli ($n = 1$), and unknown ($n = 1$). The median time to progression was 1.9 years. The probability of progression at 1 year and 2 years after PS was 36% (95% CI, 23%-53%) and 54% (95% CI, 38%-71%), respectively (Figure 4). The probability of death as a competing risk at 1 and 2 years was 10% (95% CI, 4%-25%) and 15% (95% CI, 6%-34%), respectively. The hazard ratio comparing minor versus major response was 2.13. The probability of progression at 1 year was 25% (95% CI, 12%-47%) and 55% (95% CI, 32%-81%) for patients who had major and minor response, respectively.

Discontinuation of Immunosuppressive Therapy

Ten of the 42 (24%) responders discontinued systemic immunosuppressive treatment at one point after PS. Seven responding patients died before discontinuation because of infection with ($n = 3$) or without ($n = 4$) progressive cGVHD. Another patient died of respiratory failure secondary to bronchiolitis obliterans. The probability of discontinuation of systemic immunosuppressive therapy at 1 year and 2 years after PS was 9% (95% CI, 3%-25%) and 27% (95% CI, 15%-48%), respectively (Figure 5).

Adverse Effects

All patients tolerated the PS regimen very well, without any life-threatening adverse effects. Two patients had a hypertensive episode and another developed tachycardia associated with dizziness during PS administration. None of these events necessitated hospitalization. After the completion of PS, 1 patient who had hypertension and 2 other patients (5%) later developed various infections, including

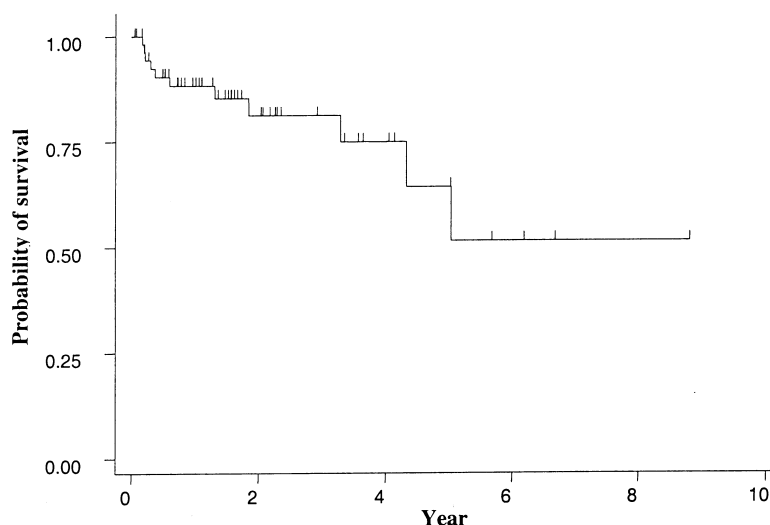


Figure 3. Kaplan-Meier probability of survival for all patients.

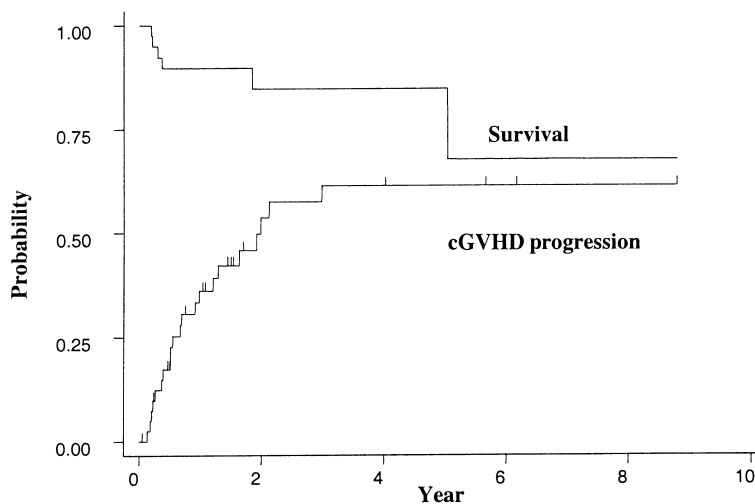


Figure 4. Kaplan-Meier probability of progression and survival after high-dose pulse methylprednisolone therapy in responding patients with chronic graft-versus-host disease (cGVHD).

cellulitis and disseminated herpes simplex (n = 1), pneumonia (n = 1), and aspergillus (n = 1). These 3 patients were already on steroids and other immunosuppressive drugs.

DISCUSSION

The optimal dose and schedule of corticosteroid treatment in aborting the acute progression of cGVHD are unknown and clinical data are very limited. Although various doses of systemic corticosteroids have been used in acute GVHD [8-10], there has been no study evaluating the role of high-dose corticosteroid regimens in the treatment of cGVHD. In a small study, 2 of 7 patients with acute GVHD responded to high-dose glucocorticoid therapy when the dosage was escalated from 5 mg/kg per day to 10 mg/kg per day [9]. This dose-response relation was not demonstrated in another study when the comparison

was made between the dosages of 2 mg/kg per day and 10 mg/kg per day [10]. Although high-dose glucocorticoid therapy is a well-accepted initial treatment for a variety of immunologically mediated diseases, including GVHD, the question of what dose of steroid should be considered high still remains to be determined.

The concept of the PS regimen was to use a lympholytic dose of steroids to try to destroy as many effector lymphocytes as possible before permanent tissue damage occurred. Glucocorticoids have different mechanisms of action depending on their dose. Low-dose glucocorticoids achieve their action completely by classic genomic effects, mediated by the glucocorticoid receptor. In addition to these well-known genomic effects, high doses of glucocorticoids interfere, via nongenomic pathways, with the process of energy metabolism crucial for the immediate and sustained activation of lymphocytes. Buttgerit and his colleagues have

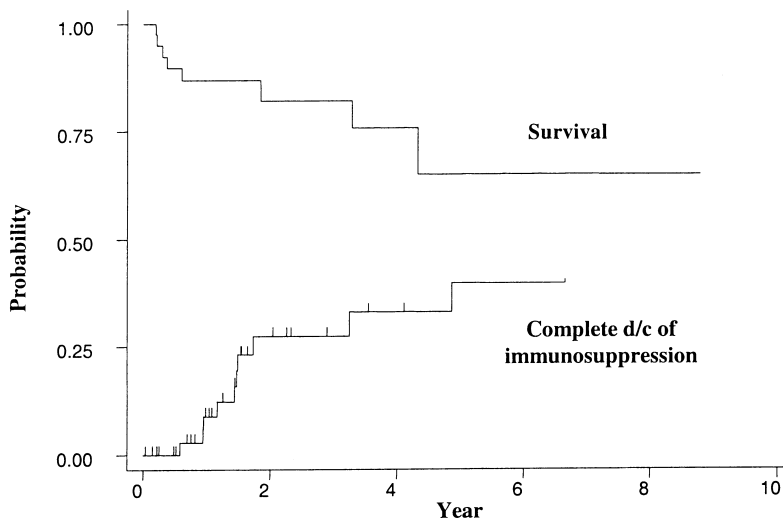


Figure 5. Kaplan-Meier probability of discontinuation (d/c) of all systemic immunosuppressive therapy and survival after high-dose pulse methylprednisolone therapy in responding patients with chronic graft-versus-host disease.

assessed the relative therapeutic importance of these nongenomic effects in pulse corticosteroid therapy by measuring the number of glucocorticoid receptor sites and glucocorticoid receptor binding affinity in peripheral blood mononuclear cells isolated from 48 healthy children and 35 patients [13]. The patients had been divided into 3 groups based on glucocorticoid treatment: 0 mg/kg (group 1), 0.01 to 0.3 mg/kg orally (group 2), and 10 to 15 mg/kg intravenous pulse therapy (group 3) of prednisolone equivalent per day. The number of receptor sites in patients without glucocorticoid treatment (group 1) was significantly lower than that of healthy volunteers. This value was further reduced in patients receiving glucocorticoid treatment. The more significant downregulation of receptor binding sites (group 3) was found after pulse therapy compared with untreated patients. These results have confirmed the previous observation in another study population reported by the same investigators [14]. It was suggested that pulse therapy doses of glucocorticoids that exceed receptor saturation have an additional effect on lymphocytes via significant receptor downregulation (nongenomic effect).

Other studies have shown that high-dose glucocorticoid treatment could diminish or prevent the acute immune response by interfering with processes, such as the rise in intracellular Ca^{2+} concentration, that are essential for the immediate and sustained activation of lymphocytes [15]. High doses of glucocorticoids affect both the activated and the resting cell populations. It has been previously demonstrated in thymocytes that glucocorticoid pretreatment of resting/quiescent cells prevents the concanavalin A-induced increase of oxygen consumption and rise in cytosolic Ca^{2+} . Consequently, quiescent glucocorticoid-treated cells are less likely to become activated during the course of the disease [16,17].

High-dose PS therapy may also turn off the lymphocyte functions through the induction of apoptotic mechanisms. In a recent study from Japan, investigators evaluated the in vivo effects of high-dose (1 g) methylprednisolone infusion on peripheral blood T-lymphocyte apoptosis induction in patients with severe autoimmune diseases [18]. DNA fragmentation was detected in peripheral blood T cells isolated from these patients after 2 and 4 hours of steroid infusion. In contrast, T cells isolated from the same patients before or 8 or more hours after infusion did not show DNA fragmentation. To support the T-cell apoptosis induction by high-dose PS therapy, peripheral blood T cells from normal subjects underwent DNA fragmentation after in vitro exposure to 2.5 to 10 $\mu\text{g}/\text{mL}$ of methylprednisolone for 30 minutes.

The results of the present study suggest that methylprednisolone treatment at 10 mg/kg for 4 days can lead to a major improvement of symptoms and signs in approximately half of the patients with severe refractory cGVHD. We have observed a high response rate (75%) using our PS regimen in cGVHD patients who were refractory to a median of 2 previous systemic immunosuppressive treatment courses. Although median time to progression of cGVHD after PS was about 2 years with occasional durable responses, subsequent progression or flare of cGVHD is concerning, particularly in those who had no or minor response to PS. Although this PS regimen was initially effective in reversing the cGVHD progression, it was not capable of switching off cGVHD completely in the majority of patients. At 3 years

after PS therapy, the probability of progression was 61%, proving that long-term control of cGVHD is clearly needed.

Perhaps the most important point of this study is the correlation between the type of response to PS and time to progression. The 30% difference in the probability of progression at 1 year after PS therapy between patients who achieve major response and those who achieve minor response suggests that better response is associated with longer time to progression. This may provide some important prognostic information for patients and physicians.

PS therapy usually was tolerated excellently, with very few immediate side effects. However, the infectious complications occurring in 3 patients after completing the therapy raise the possibility of profound immunosuppression, which may be associated with the PS regimen on top of already heavily immunosuppressed patients. It will remain unknown whether PS therapy itself or the subsequent new immunosuppressive therapy course is the primary set-up for the occurrence of these infections seen within 1 month of therapy.

The PS protocol we report here is based on the clinical experience we have gained over the past 12 years in treating patients with cGVHD. Our previous results support the use of PS over a short treatment time because little additional benefit could be obtained by a longer treatment duration or higher doses. As noted in this report, the majority of our patients, particularly those who had major responses to PS, had sustained resolution of GVHD activity. Median time to progression was almost 2 years in those who responded to PS and a subsequent course of immunosuppressive treatment. One could argue that the time to progression may also be related to the effectiveness of the immunosuppressive treatment given after PS. This is certainly a possibility, but it is not likely due to the lack of data showing that any particular salvage regimen is superior to another in the setting of progressive cGVHD.

In summary, our results demonstrate that PS is an effective and well-tolerated regimen in patients with progressive/refractory cGVHD. Timely identification of nonresponding or incompletely responding patients may allow early assignment to alternate immunosuppressive treatment. The early combination of PS with other treatment strategies including monoclonal antibodies [19-22] may further improve response rate and progression-free survival of some patients. Additional studies are warranted to test this hypothesis.

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