VOLUME 25 · NUMBER 27 · SEPTEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Study of Pentostatin in Patients With Corticosteroid-Refractory Chronic Graft-Versus-Host Disease

David A. Jacobsohn, Allen R. Chen, Marianna Zahurak, Steven Piantadosi, Viki Anders, Javier Bolaños-Meade, Meghan Higman, Jeffrey Margolis, Michele Kaup, and Georgia B. Vogelsang

From the Robert H. Lurie Comprehensive Cancer Center and Division of Hematology/Oncology/Transplant, Children's Memorial Hospital, Chicago, IL; Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; and the Rose Cancer Center, William Beaumont Hospital, Royal Oak, MI.

Submitted January 18, 2007; accepted June 11, 2007.

Presented in part at the American Society of Hematology Meeting, Atlanta, GA, December 10-13, 2005.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Address reprint requests to Georgia B. Vogelsang, MD, Division of Hematologic Malignancies, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Bunting-Blaustein Cancer Research Bldg 2M89, 1650 Orleans St, Baltimore, MD 21231; e-mail: vogelge@jhmi.edu.

© 2007 by American Society of Clinical Oncology

0732-183X/07/2527-4255/$20.00

DOI: 10.1200/JCO.2007.10.8456

ABSTRACT

Purpose
Therapy for patients with chronic graft-versus-host disease (cGVHD) is based on prolonged immunosuppression with corticosteroids. There is no standard therapy for patients whose cGVHD does not resolve with corticosteroid treatment. Pentostatin, a potent inhibitor of adenosine deaminase, has activity in acute GVHD. We examined the toxicity and efficacy of pentostatin in a prospective phase II trial in corticosteroid-refractory cGVHD.

Patients and Methods
Patients of any age were eligible. Patients received pentostatin 4 mg/m^2 intravenously every 2 weeks for 12 doses, and continued therapy as long as benefit was documented. Corticosteroid taper was begun after three doses of pentostatin. Responses were graded in real time in the skin, mouth, and liver using objective response criteria.

Results
Fifty-eight heavily pretreated (median, four prior regimens) patients (median age, 33 years) were enrolled. Results are shown as an intent-to-treat analysis. Of the 58 patients, a total of 32 (55%; 95% CI, 42% to 68%) had an objective response, as evaluated by use of a new grading scale. Infection was the most significant toxicity, with 11 grade 3 to 4 infectious events. The survival at 1 and 2 years was 78% (95% CI, 64% to 86%) and 70% (95% CI, 57% to 80%), with cGVHD with/without infection accounting for the majority of deaths.

Conclusion
Pentostatin has immunosuppressive effects that are currently being explored further for treatment of cGVHD.

J Clin Oncol 25:4255-4261. © 2007 by American Society of Clinical Oncology

INTRODUCTION

Chronic GVHD (cGVHD) is the major late complication of stem-cell transplantation (SCT). In fact, cGVHD can be thought of as a late effect of cancer therapy. Nevertheless, cGVHD has received only a fraction of the research attention of acute GVHD. Recent changes in SCT practice have made it imperative to better define and treat this disorder. The incidence of cGVHD is increasing due to increased use of donor-lymphocyte infusions, peripheral-blood stem cells, increasing age of transplant recipients, and use of more alternative donors.

Systemic corticosteroids as primary therapy for cGVHD was shown more than 20 years ago to improve survival as compared with no therapy.[1] Patients with extensive cGVHD require prolonged treatment.[2,3] There is no standard therapy for patients whose cGVHD does not resolve with administration of corticosteroids. Recently reported therapies include sirolimus,[4] mycophenolate mofetil,[5] rituximab,[6] and extracorporeal photopheresis.[7] We report the results of a phase II study using pentostatin (deoxycoformycin [Nipent]; Mayne Pharma, Paramus, NJ), a nucleoside analog that is a potent inhibitor of adenosine deaminase,[8] in patients with corticosteroid-refractory cGVHD. Our group has shown activity of pentostatin in a phase I study of corticosteroid-refractory acute GVHD.[9]

PATIENTS AND METHODS

Patient Eligibility

All patients provided informed consent. The investigator-initiated study was approved by Johns Hopkins (Baltimore, MD) institutional review board, Children's Memorial Hospital (Chicago, IL) institutional review board, and US Food and Drug Administration. Patients were required to have biopsy-confirmed, treatment-refractory cGVHD (failure of one or more

Downloaded from jco.ascopubs.org on February 16, 2010 . For personal use only. No other uses without permission.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.

immunosuppressive therapies, including corticosteroids at least equivalent to prednisone 0.5 mg/kg/d, for at least 3 months). CGVHD was active (increasing disease symptoms despite immunosuppression or returning during taper or discontinuation of immunosuppression) in all patients.

Patients of any age were eligible. Performance status was required to be Eastern Cooperative Oncology Group 0 to 2. Patients underwent a screening evaluation with physical examination, appropriate tissue biopsies, Schirmer's test, blood chemistries, and complete blood count with differential. Exclusion criteria were life expectancy $\leq$ 6 months, inability to return for follow-up, calculated creatinine clearance less than 30 mL/min/1.73 m^2, absolute neutrophil count less than 1,000 μL, active infection not responding to antibiotics, bronchiolitis obliterans as the sole manifestation of disease (excluded due to lack of uniform diagnostic and response criteria), or pregnancy or lactation.

Drug Administration

Pentostatin was administered at 4 mg/m^2 by intravenous infusion during 20 to 30 minutes in 100 to 250 mL of 5% dextrose and normal saline every 2 weeks, with intravenous hydration before and after each dose.[10]

Initially patients received 12 doses, but the protocol was modified (after patient 16) to allow patients still showing improvement at the 6-month evaluation to continue pentostatin every 3 to 4 weeks until therapeutic plateau, after noting that some patients were still improving at end of therapy and one experienced progression off therapy. The dose was modified for decreases in creatinine clearance: if the estimated glomerular filtration rate was less than 50 mL/min/1.73 m^2 and more than 30 mL/min/1.73 m^2, one half the original dose was administered; if the estimated glomerular filtration rate was less than 30 mL/min/1.73 m^2, additional administration of drug was withheld until renal function improved. The dose was reduced by 25% if grade 3 hematologic toxicity (absolute neutrophil count range, 500 to 1,000 d/L) occurred. Patients who had neutropenia and fever, or whose platelet count decreased below 20,000/μL, had future doses of pentostatin reduced by 50%. Pentostatin was withheld if the patient had severe infection.

Patients included in this study received pentostatin as their only new intervention. The major recommendation of the study was to wean patients off of corticosteroids by 6 to 8 weeks and to continue administration of the calcineurin inhibitor. Thus, the corticosteroid dose was tapered approximately 25% every 7 days after three doses of pentostatin if the patient had stability or minor response and patients continued receiving calcineurin inhibitor unless there was drug toxicity. Other immunosuppressive medications were tapered on an individual basis.

Supportive Care

Patients received *Pneumocystis jiroveci* prophylaxis with trimethoprim/sulfamethoxazole or equivalent, antiviral prophylaxis with acyclovir or equivalent, and antibacterial prophylaxis with penicillin or equivalent.

Clinical End Points

Patients were evaluated at 3-month intervals, including scoring in six domains (Table 1): lichenoid rash, scleroderma, fascial involvement, oral symptoms, oral examination findings, and liver disease. These domains were chosen to make the evaluation as objective as possible. Because many other factors in addition to cGVHD could influence symptoms (eg, nausea from an antibiotic or weight gain from corticosteroids), we did not include other categories in our grading, but did collect data prospectively on changes. Likewise, we did not include lung disease and dry eyes, for which it is unclear that organ damage can be repaired even if the underlying immunologic process improves. Patients were assigned scores of 0 (none) to 3 or 4 (worst) points in each domain. A total score was calculated. The following response definitions were used: major response (improvement by at least two points in one domain with no worsening in any domain), minor response (improvement by at least one point in one domain with no worsening in any domain), and progression (worsening in any domain, including those not used in scoring). A major or minor response constituted a response. Patients were assessed by the study principal investigators. A detailed symptom list and physical examination findings were recorded by the study nurse. These two forms were used to confirm responses. In the rare case of a discrepancy, clinic notes were used to clarify ambiguity. Each patient's response is shown at 3 months and at his or her final assessment. The latter represents the maximum response for patients with persistent improvement. Patients with an improvement but later worsening were considered to have progressive disease. Duration of response after therapy was not an end point of this study, and cGVHD scores were not monitored prospectively off study.

Table 1. Criteria Used to Score Patients at 3-Month Assessments

Skin lichenoid/erythematous lesions
0. No rash
1. Rash involves < 25% of skin
2. Rash involves > 25% to 50% of skin
3. Rash involves > 50% to 75% of skin
4. Rash involves > 75% of skin
Skin scleroderma
0. Normal skin
1. Thickened with pockets of normal skin
2. Thickened over majority of skin
3. Thickened, unable to move
4. Hidebound, unable to pinch
Fascial
0. Normal
1. Tight with normal areas
2. Tight
3. Tight, unable to move
Mouth symptoms
0. No symptoms
1. Food sensitivity
2. Pain requiring narcotics
3. Unable to eat
Oral examination
0. Normal
1. Erythema
2. Lichenoid changes
3. Ulcerations
Liver, mg/dL
0. Bilirubin < 2
1. Bilirubin > 2 and < 5
2. Bilirubin > 5 and < 10
3. Bilirubin > 10 and < 15
4. Bilirubin > 15

All patients were evaluated for toxicity and response. If a patient went off study due to toxicity or protocol violation, the last evaluation done for the patient was used to determine response. Toxicity was scored using the National Cancer Institute Common Toxicity Criteria, Modified for Bone Marrow Transplantation.

Criteria for Removal From Protocol

Study therapy and interventions were discontinued early if cGVHD progressed after 6 or more weeks of treatment. Patients with a mixed response at 6 weeks on study could continue on study at the discretion of the treating physician. Patients not showing improvement by 3 months were taken off study and were considered to have experienced treatment failure. Patients who experienced grade 3 to 4 nonhematologic toxicity attributable to pentostatin and those noncompliant with study medications were removed from study.

Statistical Considerations

The primary statistical end point was overall response rate. Response was based on comparison of the patient's final on-study assessment versus his or her initial evaluation. For purposes of sample size estimation, a 50% response rate was assumed. A sample size of 50 was required to estimate response rate with a 95% CI of $\pm$ 15% or less.

A secondary outcome was change in individual organ system scores pre- and poststudy. Changes were calculated as post-treatment minus pretreatment value. Boxplots[11] have data values jittered in the x and y directions so overlaid values are separated. The Wilcoxon signed rank test[12] was used to test

Downloaded from jco.ascopubs.org on February 16, 2010 . For personal use only. No other uses without permission.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.

if median change in total score was significantly different from zero. The sign test[12] was used when distribution of changes in organ scores appeared asymmetric, contrary to assumptions required by the Wilcoxon signed rank test. This method was used to test the null hypothesis that changes were equally likely to be positive or negative.

Factors associated with response were selected based on cross tabulations and logistic regression modeling.[13] Cross tabulations were analyzed using χ^2 or Fisher's exact tests where appropriate. Computations were performed using Statistical Analysis System (SAS Inc, Cary NC).[14] R[15] was used for graphics. *P* values are two sided and reported without formal adjustment for multiple comparisons. Survival was measured from start of study drug until April 2006.

RESULTS

Patients

Table 2 summarizes clinical characteristics of the 58 patients enrolled, including five patients reported previously.[16] Median age was 33 years (range, 5 to 64 years). Patients had received a median of 19 months (range, 3 to 120 months) of therapy and a median of four drug combinations (range, one to seven drug combinations), including corticosteroids and one calcineurin inhibitor before enrolling. Other immunosuppressants after which patients had experienced treatment failure at any time before starting study included mycophenolate mofetil (n = 44), thalidomide (n = 14), hydroxychloroquine (n = 13), psoralen plus UV light of A wavelength (n = 12), extracorporeal photopheresis (n = 12), rapamycin (n = 9), etretinate (n = 8), daclizumab (n = 6), azathioprine (n = 4), flutamide (n = 1), clofazimine (n = 1), etanercept (n = 1), rituximab (n = 1), antithymocyte globulin (n = 1), and cyclophosphamide (n = 1). Forty-three patients (74%) were taking corticosteroids and 43 patients (74%) were taking calcineurin inhibitor at time of study entry. As summarized in Table 3, patients had significant manifestations of cGVHD. Almost all patients had skin disease, and most had range of motion limitation. More than half of the patients had oral disease and GI symptoms, including dysphagia, nausea, vomiting, and/or diarrhea.

Table 2. Patient Characteristics

Characteristic		No. of Patients
Total No.		588
Age, years		
Median	33	
Range	5-64	
Sex		
Male		35
Female		23
Diagnoses		
CML		15
AML/MDS		9
ALL		11
NHL		7
MM		5
CLL		1
AA		6
Hemoglobinopathy		3
FHLHS		1
Type of transplantation		
HLA-identical or 5/6 sibling BMT		26
HLA-identical sibling BMT with DLI or boost		4
HLA-identical sibling PBSC		9
Matched-unrelated donor BMT		16
Matched-unrelated donor PBSC		1
Haploidentical or 5/6 parent PBSC		2

Abbreviations: CML, chronic myeloid leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin's leukemia; MM, multiple myeloma; CLL, chronic lymphocytic leukemia; AA, aplastic anemia; FHLHS, familial hemophagocytic lymphohistiocytosis syndrome; BMT, bone marrow transplantation; DLI, donor lymphocyte infusion; PBSC, peripheral-blood stem cell.

Response

Of 58 patients, a total of 32 patients (55%; 95% CI, 42% to 68%) had an objective response. Response was major in 31 patients and minor in one patient. Of the 32 with an objective response, eight came off study because of complications: four complications were related to pentostatin (nausea/vomiting in two patients, renal toxicity in one patient, and fatigue in one patient) and four complications were attributed to other causes. An additional three responding patients came off study because of protocol violations (one patient did not meet patient-entry criteria, one patient refused to return for follow-up, and one patient was noncompliant with prophylactic antibiotics and other medications). Patients with a response received a median of 12 doses (range, one to 32 doses).

Two patients never returned for follow-up and are classified as having no response. There was no response data available for them. Total severity scores for the 56 assessable patients were lower post-therapy, with a median change of −3 points (range, −8 to 5 points; Wilcoxon signed rank test statistic, $P < .0001$). Post-treatment, 10.3% (six of 58 patients) had total scores of zero. Total scores improved in 38 of 58 patients (65.5%), worsened in 13 of 58 patients (22.4%), remained constant in five of 58 patients (8.6%), and were not assessable in two of 58 (3.5%). Six patients had improved scores but are classified as having progressive GVHD due to progression of disease in one domain, despite improvement in others (see definitions of response in

Table 3. Chronic GVHD Characteristics at Study Entry

Characteristic	No. of Patients	%
Skin involvement*	54	93
Decreased ROM*	39	67
Oral involvement*	39	67
GI symptoms*†	32	55
Liver involvement*	6	10
Dry eyes*	28	48
PFT < 50% predicted*	6	10
Karnofsky/Lansky performance status < 50%	7	12
Poor prognosis factors		
Progressive onset	20	34
Thrombocytopenia	7	12
Extensive skin involvement	15	26
1 poor prognosis factor	5	9
≥ 2 poor prognosis factors	16	28

Abbreviations: GVHD, graft-versus-host disease; ROM, range of motion; PFT, pulmonary function test.
*Median number of these organs affecting each patient at study entry was 4 (range, 1-6 organs).
†Include dysphagia, nausea, vomiting, and/or diarrhea.

Downloaded from jco.ascopubs.org on February 16, 2010 . For personal use only. No other uses without permission.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.

the previous paragraph). A total of 26 (45%; 95% CI, 32% to 58%) patients had either no response or had worsening cGVHD. Five of these patients had had either stable disease or a response at 3 months, and then progression by their 6- to 9-month visit.

Changes in scores for individual domains are summarized in Figure 1. With the exception of liver, approximately 30% of the patients for each of the organ systems were rated zero before and after therapy. The largest improvement was seen in lichenoid skin: 27 (69%) of 39 affected patients showed improvement. The scleroderma, fascial, and mouth symptom domains were similar in numbers of affected patients experiencing improvement (52% to 57%), no change (31% to 38%), or increasing severity score (8% to 15%). Oral examination scores improved in 24 (62%) of 39 patients and worsened in 10 patients (26%). Of six patients with liver involvement, scores for four patients improved and scores for two patients worsened. Two patients without liver involvement at the start had worsening in this domain. Changes in scores for the skin lichenoid, skin scleroderma, fascial, and mouth symptom domains were significant. Sign-test statistics (M) indicate that changes were more likely in the negative direction: skin lichenoid, $M = -10.5$, $P = .0003$; skin scleroderma, $M = -8.5$, $P = .0005$; fascial, $M = -7$, $P = .009$; mouth symptoms, $M = -8$, $P = .0015$; and oral examination, $M = -7$, $P = .02$.

Table 4 lists initial, 3 month, and final score in each domain, for all patients and for patients with initial involvement in each domain. The time at the final score varied, and corresponds to when patients had their last infusion of study drug. The median time on study for those with overall response was 175 days (range, 1 to 701 days); for those who experienced progression, the median time on study was 74 days (range, 1 to 408 days).

Factors Affecting Response

We sought to determine whether age or poor-prognosis risk factors[17] affected response. In the group younger than the median age of 33 years, 20 of 26 patients (77%; 95% CI, 56% to 91%) experienced

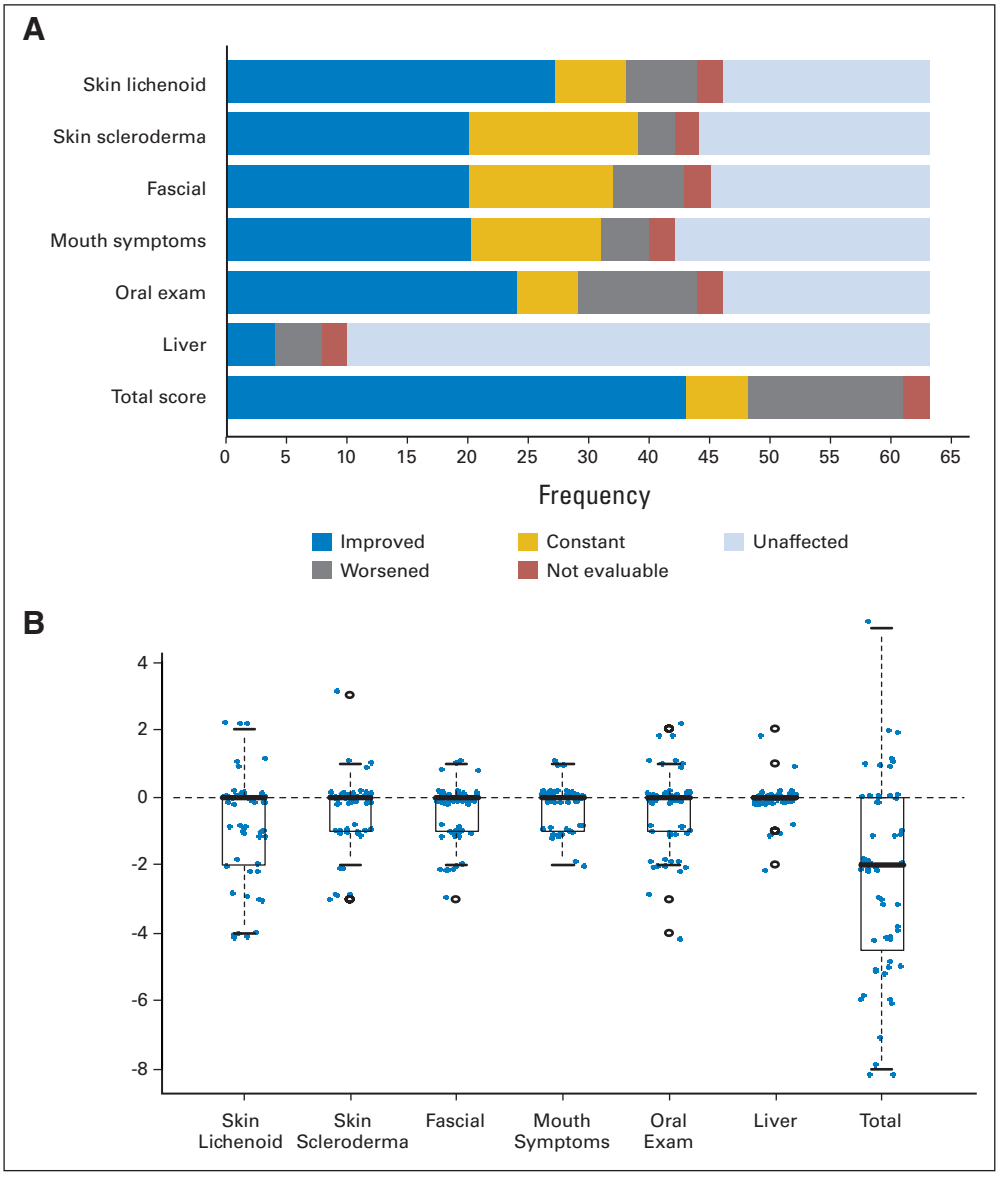

Fig 1. (A) Distribution of change in domains and total score. (B) Magnitude of change (domains and total) for 56 assessable patients. Negative values represent improvement. Boxplot length is interquartile range (IQR); median is horizontal line within boxplot; adjacent values (lines extending from boxplot) are upper quartile + 1.5 × IQR and lower quartile − 1.5 × IQR. Actual values are in red; (○) boxplot representation next to values considered outliers.

Downloaded from jco.ascopubs.org on February 16, 2010 . For personal use only. No other uses without permission.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.

Table 4. Individual Domain Scores at Start, 3 Months, and End of Study

Domain	Start			3 Months			End		
	No. of Patients	Median	Interquartile Range	No. of Patients	Median	Interquartile Range	No. of Patients	Median	Interquartile Range
Lichenoid									
All patients	58	1	0-3	56	0	0-1	56	0	0-1
Active patients	39	2	1-4	38	0.5	0-1	38	0	0-1.5
Scleroderma									
All patients	58	1	0-4	56	1	0-3	56	1	0-2
Active patients	37	4	1-4	36	2.5	1-4	36	1	1-3
Fascial									
All patients	58	2	0-3	56	1	0-2	56	1	0-2
Active patients	37	2	2-3	36	1.5	1-2	36	1	1-2
Mouth symptoms									
All patients	58	1	0-1	56	0	0-1	56	0	0-1
Mouth symptoms	33	1	1-1	32	0	0-1	32	0	0-1
Oral examination									
All patients	58	2	0-2	56	0	0-2	56	0	0-2
Active patients	34	2	2-2	33	2	0-2	33	0	0-2
Liver									
All patients	58	0	0-0	56	0	0-0	56	0	0-0
Active patients	6	1.5	1-3	6	0.5	0-2.5	6	1	0-3.5
Total*	58	7	5-8	56	4	2-6.5	56	3	1-6

NOTE. Values are shown both for all patients in that particular domain and for patients with initial involvement in that particular domain. Two patients never returned for follow-up after the initial visit. The study was not powered to examine activity of pentostatin within each domain.
*Sum of all domains at each time point for all patients.

a response and in those 33 and older, 12 of 32 patients (37.5%; 95% CI, 21% to 56%) experienced a response; odds ratio for response in those younger than 33 years was 5.6 (95% CI, 1.6 to 16.7; $P = .004$). Extensive skin involvement at diagnosis of cGVHD was associated with a lower probability of response (odds ratio, 0.63; 95% CI, 0.19 to 2.05) that was not statistically significant. The type of onset (progressive, de novo, quiescent) did not influence rate of response.

Additional Clinical Benefits

Patients received a median corticosteroid dose (prednisone or equivalent) of 25 mg/d (range, 0 to 450 mg/d) at the time of the first dose of pentostatin, and a median corticosteroid dose of 5 mg/d (range, 0 to 800 mg/d) at the final pentostatin dose. When we compared final to initial corticosteroid dose, there were five patients who had an increase in dose, compared with 28 patients who had a decrease in dose. Eleven patients had no change in dose. A total of 26 patients either were taking no corticosteroids or were taking physiologic replacement doses at completion of therapy with pentostatin.

Data were collected at each patient visit on other symptoms potentially due to cGVHD. Although not formally included in the grading scale, responses were also seen in these symptoms. Of the 32 patients with GI symptoms (nausea, vomiting, diarrhea), 21 had improvement/resolution of GI symptoms on treatment. In the six patients with pulmonary function tests less than 50% of predicted, four had their immunosuppression tapered/discontinued.

Toxicity and Mortality

Immediate drug toxicity was minimal, with nausea as the main adverse effect reported. All severe adverse events reported in the study are listed in Table 5. A total of 17 of 58 patients (29%; 95% CI, 18% to 42%) experienced a severe adverse event possibly related to pentostatin. A total of 11 infectious complications, reported as severe adverse events, were possibly related to pentostatin. No patient needed a central venous line to receive study drug.

The survival at 1 and 2 years was 78% (95% CI, 64% to 86%) and 70% (95% CI, 57% to 80%), respectively. For the 39 surviving patients, the median follow-up is 49 months (range, 10 to 68 months). Nineteen of the 58 patients have died. The primary cause of death was cGVHD with noninfectious complications (n = 8), followed by cGVHD with infection (n = 5), hemorrhage (n = 1), pulmonary failure (n = 1), and relapse (n = 4). Two of the four patients who died as a result of relapse had responded to therapy with pentostatin (including one patient who was already experiencing relapse when enrolled).

DISCUSSION

The last 20 years have produced remarkable improvements in SCT, with one notable exception: treatment of patients with cGVHD has not changed substantially from the clinical trial defining corticosteroids as the standard for initial therapy.[1] The message from the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease (NIH Consensus Conference on cGVHD) is clear: cGVHD is a major impediment to the success of transplantation. Both therapy and basic biology of cGVHD deserve increased attention.

This article reports the use of the pentostatin in the treatment of cGVHD. The findings are notable for several reasons. First, the patients were heavily pretreated. Reports of other salvage therapy have seen few responses in similar cohorts of heavily pretreated

Downloaded from jco.ascopubs.org on February 16, 2010 . For personal use only. No other uses without permission.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.

Table 5. SAEs

Type of AE	Attribution			
	Possibly Related*		Not Related	
	No. of AEs	No. of Doses†	No. of AEs	No. of Doses†
Infection				
Bacteremia/sepsis (coagulase-negative *Staphylococcus*, *Serratia*)	3	3, 6, 9		
Other bacterial syndrome	4	1, 2, 7, 8		
Documented fungal infection (*Aspergillus*, *Candida glabrata*)	2	5, 7	1	1
Documented viral infection (herpes varicella-zoster)	2	6, 6		
CNS: ptosis, seizure, suicide attempt	2	1, 4	1	6
Renal insufficiency	2	2, 6	1	3
GI: pancreatitis, abdominal pain, appendicitis, pancreatitis, ulcers	1	12	4	1, 1, 5, 7
Endocrine: adrenal insufficiency	1	6		
Dermatology: erythema			1	1
Metabolic: hyperglycemia/dehydration			1	4
Progressive malignancy			1	7
Constitutional: lethargy			1	12

NOTE. All adverse events graded 3 or higher according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 3.0 are included, regardless of attribution.
Abbreviations: SAE, severe adverse event; AE, adverse event.
*No SAEs were deemed probably or definitely attributable to pentostatin on this study.
†No. of doses of pentostatin the patient received before the SAE occurred. In some cases, pentostatin had been withheld or discontinued for up to 30 days before development of the SAE.

patients.[4,7] Thus, the response rate of 55% is encouraging. The response rate is based on objective data. One of the difficulties in evaluating treatment trials in cGVHD has been the relatively qualitative, investigator-dependent response criteria. This trial used predefined objective response criteria that were applied in real time. Although a limitation of these criteria is their lack of validation, they are likely better than the vague qualitative criteria frequently used, although the nonblinded design of the current trial cannot eliminate the possibility of assessor bias. The length of follow-up of our patients also exceeds the short-term outcomes recommended for phase II by the NIH Consensus Conference on cGVHD.[18]

Second, there appears to be an age effect. This must be interpreted with caution, given that too few patients were included in this study to perform a multivariate analysis required to determine with certainty that age was the most significant factor. Could this difference in response rate be due to different effects of pentostatin on the young, relatively plastic immune system versus a mature immune system? To explore this question requires a better understanding of the immunology of cGVHD and the effects of pentostatin on the immune system. The Pediatric Blood and Marrow Transplant Consortium has an ongoing trial examining pentostatin as salvage therapy in children with corticosteroid-refractory cGVHD based on these findings.

Although this study is relatively large for a salvage therapy trial, it was not powered to explore the effects of pentostatin on specific organ manifestations of cGVHD. The scoring system used was designed to reflect the distribution of organs involved in cGVHD, where 65% to 80% of patients have skin involvement,[19] making skin the most commonly involved organ by far. Similar to our trial, the NIH Consensus Conference on cGVHD recommended grading the skin at three levels (erythema, moveable sclerosis, and nonmoveable sclerosis) because patients can have improvement or worsening in any or all of these manifestations.[20] However, caution must be used in generalizing these results to treatment of patients with less common manifestations of cGVHD and until the new scoring systems are validated in additional clinical studies.

The toxicity profile of pentostatin in this study was modest. The two toxicities of concern were nausea/vomiting and infection, particularly fungal infection. The late nausea and vomiting was unexpected and proved to be debilitating in those affected. After the trial started, aprepitant, which is effective for delayed nausea, was introduced. It is hoped that it will prove beneficial for patients receiving pentostatin. The fungal infections also proved difficult to treat, as in the phase I study using pentostatin in corticosteroid-refractory acute GVHD.[9] This complication became more manageable during the course of this study after the introduction of less toxic, effective antifungal agents. Patients with a prior history of significant fungal infections need close monitoring if treated with pentostatin. As in all therapies, another factor that will influence its ultimate role in treatment is the cost and charges associated with delivery.

Although not a primary end point of the study, overall survival at 1 year was 78%. In our retrospective study of the development of a cGVHD prognostic model, we found disease-specific survival for corticosteroid-refractory cGVHD to be 38%.[17] In studies using newer approaches, 1-year survival was published only in the report by Couriel et al[7] with the use of extracorporeal photopheresis as 53%. Although direct comparison of the current study with historical data and recently reported studies is not possible, these results justify future studies to test the hypothesis that pentostatin may improve survival of patients with corticosteroid-refractory cGVHD. In addition, durability of responses after

Downloaded from jco.ascopubs.org on February 16, 2010 . For personal use only. No other uses without permission.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.

discontinuation of therapy will be an important end point for future investigation. It is hoped that this study, along with several others and the NIH Consensus Conference on cGVHD, will spur greater research interest in cGVHD.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment: N/A **Leadership:** N/A **Consultant:** N/A **Stock:** N/A **Honoraria:** David A. Jacobsohn, SuperGen; Allen R. Chen, SuperGen; Javier Bolaños-Meade, SuperGen; Georgia B. Vogelsang, SuperGen **Research Funds:** David A. Jacobsohn, SuperGen; Georgia B. Vogelsang, SuperGen **Testimony:** N/A **Other:** N/A

AUTHOR CONTRIBUTIONS

Conception and design: David A. Jacobsohn, Jeffrey Margolis, Georgia B. Vogelsang
Provision of study materials or patients: Allen R. Chen, Viki Anders, Georgia B. Vogelsang
Collection and assembly of data: David A. Jacobsohn, Allen R. Chen, Viki Anders, Michele Kaup
Data analysis and interpretation: David A. Jacobsohn, Marianna Zahurak, Steven Piantadosi, Javier Bolaños-Meade, Meghan Higman, Georgia B. Vogelsang
Manuscript writing: David A. Jacobsohn, Javier Bolaños-Meade, Meghan Higman, Georgia B. Vogelsang
Final approval of manuscript: David A. Jacobsohn, Allen R. Chen, Marianna Zahurak, Steven Piantadosi, Viki Anders, Javier Bolaños-Meade, Meghan Higman, Jeffrey Margolis, Michele Kaup, Georgia B. Vogelsang

REFERENCES

1. Sullivan KM, Shulman HM, Storb R, et al: Chronic graft-versus-host disease in 52 patients: Adverse natural course and successful treatment with combination immunosuppression. Blood 57: 267-276, 1981

2. Koc S, Leisenring W, Flowers ME, et al: Therapy for chronic graft-versus-host disease: A randomized trial comparing cyclosporine plus prednisone versus prednisone alone. Blood 100:48-51, 2002

3. Stewart BL, Storer B, Storek J, et al: Duration of immunosuppressive treatment for chronic graft-versus-host disease. Blood 104:3501-3506, 2004

4. Johnston LJ, Brown J, Shizuru JA, et al: Rapamycin (sirolimus) for treatment of chronic graft-versus-host disease. Biol Blood Marrow Transplant 11:47-55, 2005

5. Kim JG, Sohn SK, Kim DH, et al: Different efficacy of mycophenolate mofetil as salvage treatment for acute and chronic GVHD after allogeneic stem cell transplant. Eur J Haematol 73:56-61, 2004

6. Cutler C, Miklos D, Kim HT, et al: Rituximab for steroid-refractory chronic graft-versus-host disease. Blood 108:756-762, 2006

7. Couriel DR, Hosing C, Saliba R, et al: Extracorporeal photochemotherapy for the treatment of steroid-resistant chronic GVHD. Blood 107:3074-3080, 2006

8. Saven A, Piro L: Newer purine analogues for the treatment of hairy-cell leukemia. N Engl J Med 330:691-697, 1994

9. Bolaños-Meade J, Jacobsohn DA, Margolis J, et al: Pentostatin in steroid-refractory acute graft-versus-host disease. J Clin Oncol 23:2661-2668, 2005

10. Grever M, Kopecky K, Foucar MK, et al: Randomized comparison of pentostatin versus interferon alfa-2a in previously untreated patients with hairy cell leukemia: An intergroup study. J Clin Oncol 13:974-982, 1995

11. Tukey JW: Exploratory Data Analysis. Reading, MA, Addison-Wesley, 1977

12. Lehmann EL: Nonparametrics: Statistical Methods Based on Ranks. San Francisco, CA, Holden-Day, 1975

13. Cox DR: The Analysis of Binary Data. London, United Kingdom, Methuen, 1970

14. SAS Institute Inc: SAS/STAT Users Guide (Volume 2): Statistics, Version 8. Cary, NC, SAS Institute Inc, 1999

15. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria, R Statistical Foundation for Statistical Computing, 2004

16. Goldberg JD, Jacobsohn DA, Margolis J, et al: Pentostatin for the treatment of chronic graft-versus-host disease in children. J Pediatr Hematol Oncol 25:584-588, 2003

17. Akpek G, Zahurak ML, Piantadosi S, et al: Development of a prognostic model for grading chronic graft-versus-host disease. Blood 97:1219-1226, 2001

18. Martin PJ, Weisdorf D, Przepiorka D, et al: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. Design of Clinical Trials Working Group Report. Biol Blood Marrow Transplant 12:491-505, 2006

19. Lee SJ, Vogelsang G, Flowers ME: Chronic graft-versus-host disease. Biol Blood Marrow Transplant 9:215-233, 2003

20. Pavletic SZ, Martin P, Lee SJ, et al: Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biol Blood Marrow Transplant 12:252-266, 2006

Downloaded from jco.ascopubs.org on February 16, 2010 . For personal use only. No other uses without permission.
Copyright © 2007 by the American Society of Clinical Oncology. All rights reserved.