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Randomized Clinical Trial of Thalidomide, Cyclosporine, and Prednisone Versus Cyclosporine and Prednisone as Initial Therapy for Chronic Graft-Versus-Host Disease

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ABSTRACT

Chronic graft-versus-host disease (CGVHD) is a major cause of morbidity following allogeneic bone marrow transplantation. Thalidomide is active in salvage therapy for high-risk or resistant CGVHD. In a prospective randomized trial, we tested initial therapy with thalidomide. Patients with extensive CGVHD were randomized to receive either cyclosporine and alternate-day prednisone (n = 27, no-thalidomide [no-thal] group) or cyclosporine, prednisone, and thalidomide (200-800 mg/day; n = 27, thal group). Although most patients responded, initial therapy with thalidomide did not improve control of CGVHD. Response rates were 83% versus 89% at 2 months (P = .7), 88% versus 84% at 6 months (P > .8) and 85% versus 73% at 1 year (P = .5) in the thal and no-thal groups, respectively. Multivariate analysis revealed related donor transplant (odds ratio [OR] = 11.3; P =.03) and de novo or quiescent onset of CGVHD (OR = 7.7; P =.04) to be significant predictors of good early response, whereas a platelet count of ≥100,000/μL was a significant predictor of good response (OR = 10.4; P =.04) at 1 year. Survival for the thal and no-thal groups was similar at 1 year (66% versus 74%) and 2 years (66% versus 54%, P = .85). Multivariate analysis revealed progressive onset CGVHD (relative risk [RR] = 4.2; P =.01), unrelated donor (RR = 5.7; P < .01), sex mismatch (RR = 7.9; P < .01), and platelet counts of <100,000/μL (RR = 3.8; P = .01) as significant predictors of poorer survival. These data suggest that despite a high response rate (79% response and 53% complete response) and encouraging survival rates (70% at 1 year and 60% at 2 years), thalidomide offers no clinical benefit when incorporated into initial therapy for CGVHD. The value of thalidomide as salvage therapy requires further study.

KEY WORDS

Chronic graft-versus-host disease • Thalidomide • Randomized clinical trial

INTRODUCTION

Chronic graft-versus-host disease (CGVHD) is a late complication of bone marrow transplantation (BMT) characterized by a connective tissue–like disease that usually, but not always, occurs more than 100 days following BMT. Clinically, CGVHD may be manifested by involvement of the skin, oral mucosa, gastrointestinal tract, eyes, liver, lungs, and joints [1-4]. CGVHD develops in 30% to 60% of transplantation survivors [5,6] and remains a major cause of morbidity and mortality following allogeneic BMT. The major cause of death in patients with CGVHD is infection due to continued immunodeficiency [4,7]. Poor prognostic factors that have been identified include thrombocytopenia (platelet count, <100,000/μL), increased age, lichenoid skin pathology, liver involvement, and progressive presentation of CGVHD [1,8] (CGVHD developing before resolution of acute GVHD).

Prednisone alone or in combination with other immunosuppressive agents has been the standard treatment of CGVHD [6,9]. Thalidomide has also been investigated as an immunosuppressive agent active in the therapy of CGVHD [5,10,11], primarily as a salvage agent in patients with CGVHD resistant to other therapies or in high-risk patients [10,11]. Thalidomide's role in early therapy of CGVHD is not yet established. This study was designed to test the efficacy of initial CGVHD therapy with thalidomide in addition to cyclosporine and alternate-day prednisone in an open label, prospective randomized trial. We report an analysis of the response rate and survival in addition to a

comparison of the frequency of complications including infections in patients treated with and without thalidomide.

METHODS

Eligibility Criteria

Patients who underwent allogeneic BMT at the University of Minnesota between September 1993 and April 1999 and developed extensive CGVHD were eligible for inclusion in the trial. Extensive CGVHD was defined as involvement of 1 or more of the following organ systems: generalized skin involvement (≥50% body surface area), liver involvement (bilirubin, ≥3 mg/dL), positive Schirmer's test, histologically proven CGVHD of the oral mucosa, lung dysfunction with bronchiolitis obliterans, and gastrointestinal involvement with malabsorption and/or weight loss unexplained by other etiologies. High-risk CGVHD was defined as the presence of 1 or more of 3 risk factors: progressive onset, platelet count of <100,000/μL, and bilirubin level of ≥3 mg/dL. Fifty-four patients were enrolled and randomized. Patients were excluded if they had acute complications resulting in a life expectancy of <1 month, were aged <2 or >60 years, had an inability to take oral medications, had peripheral neuropathy, or were pregnant or intended to become pregnant. Patients were instructed about the hazards of birth defects associated with prenatal exposure to thalidomide, and sexually active patients were required to use effective contraception while taking thalidomide. Before randomization, patients were stratified into cohorts according to whether they had received related donor or unrelated donor marrow. Patients were randomly assigned to the thalidomide (thal) arm or no-thalidomide (no-thal) arm. Blocked randomization using block sizes of 4 and 6 was carried out. All patients or their parents/guardians gave signed informed consent according to guidelines approved by the University of Minnesota Institutional Review Board. Thalidomide was supplied by Celgene Corporation (Warren, New Jersey) under terms of a Food and Drug Administration Investigational New Drug approval issued to the investigators (D.J.W.).

Treatment Plan

Beginning at the time of randomization, all patients received initial therapy with high-dose methylprednisone. Methylprednisone was given at a dose of 15 mg/kg as an intravenous injection weekly for 8 weeks. Patients assigned to the thal arm received prednisone, cyclosporine, and thalidomide from the time of randomization. Those assigned to the no-thal arm received prednisone and cyclosporine. The initial dosage of thalidomide was 50 mg 4 times a day in adult patients and 0.75 mg/kg 4 times a day in pediatric patients. Dosage was increased as tolerated at 2 to 4 week intervals to a maximum of 200 mg 4 times a day in adults and 3 mg/kg 4 times a day in pediatric patients. Thalidomide levels were not monitored. Prednisone was given at a dosage of 0.5 mg/kg by mouth on alternate days and cyclosporine was started at 6.25 mg/kg by mouth twice daily (or 1.5 mg/kg intravenously twice daily) with the dosage being modified to maintain trough levels >200 ng/mL. In patients with no response to the initial 8 weeks of therapy or with disease progression after initial stabilization or response, methylprednisone was given at a dosage of 15 mg/kg per day intravenously for 5 days, and oral prednisone was increased to 1 mg/kg per day by mouth for 6 weeks, then tapered over a 3-month period to 0.5 mg/kg per day on alternate days. Therapy was continued until 9 months following the last clinical evidence of active CGVHD, followed by a taper over 2 to 3 months. In persistent or refractory disease, crossover to the thal arm was permitted, but only after 6 months of assigned therapy. All subjects randomized were analyzed as intention-to-treat in their assigned treatment groups.

Measurement of Response

Patients were evaluated for response to therapy at 2 months, 6 months, and 1 year from randomization. Because patients did not always return to the transplantation center on the scheduled dates, window periods for evaluation were used to maximize the completeness of evaluation. For the 2-month visit, the evaluation window period was between 1 and 3 months from randomization. For the 6-month and 1-year visits, window periods of 4 to 9 months and 9 to 16 months, respectively, were used. All patients included in the study were randomized at least 6 months prior to study termination. The median follow-up of surviving patients was 22 months (range, 6-58 months).

Response to therapy was graded as complete response (CR), defined as resolution of all signs and symptoms of CGVHD. Partial response (PR) was defined as improvement in 1 or more organs of involvement and no evidence of worsening in any organ. Flare was defined as PR or CR followed by worsening of CGVHD to a severity less than that at baseline evaluation. No response was defined as either progression of CGVHD to worse than at baseline evaluation or no improvement in CGVHD after 6 months of therapy. Prevalence of CGVHD was defined as the proportion of all patients with active CGVHD among surviving patients. Improvement or worsening of disease was determined through both subjective and objective criteria. Subjective criteria were symptomatic changes in cough, dyspnea, anorexia, nausea, vomiting, diarrhea, arthralgia, or dry eyes. Objective criteria included physical exams of skin and oral mucosa, weight measurements, liver function tests, pulmonary function tests, Schirmer's test, biopsies, and radiological studies. Patients who had no response or flare before they died were included at subsequent time points as nonresponders or treatment failures.

STATISTICAL ANALYSIS

The study was designed as a prospective randomized trial. The expected high incidence of complications caused by thalidomide (chiefly constipation and somnolence) precluded blinding of the study drug, so no placebo therapy was used. However, data collection, grading of response, and, importantly, statistical analysis were performed without knowledge of treatment-group assignment. Analysis of response and survival were performed before any examination of side effects to maintain the blinding during analysis.

Prestudy Sample Size and Power Projections

The primary endpoint of the study was response to treatment; the secondary endpoint was overall survival. To

detect a 20% difference in response (presuming a response rate of 65% in the control arm) with 80% power at α of 0.05, a sample size of 134 patients (half randomized to each arm) was needed. However, after accrual of 54 randomized patients, this blinded interim analysis was performed. Because both treatment arms had response rates higher than projected, with only a 12% difference in response between the 2 treatment arms, recalculation of the sample size to detect a >20% difference would have necessitated an added enrollment of 104 patients. This study size was unworkable, so the study was closed.

Response to Therapy

Pearson's chi-square test was employed to compare the proportion of subjects who responded to therapy with those who did not (complete and partial response versus no response and flare) at 2 months, 6 months, and 1 year after randomization. The Fisher exact test was used when the expected cell count was less than 5.

Predictors of Response

Thirteen potential predictors were evaluated. These included treatment arm, recipient age at transplantation, sex of recipient and donor, cytomegalovirus serologic status of recipient and donor, type of transplant (allogeneic sibling versus unrelated donor), HLA mismatch, prior presence and clinical grade of acute GVHD, onset of CGVHD (de novo, progressive, quiescent), organ involvement with CGVHD (eyes, mouth, skin, lungs, gastrointestinal tract, liver), white blood cell count, platelet count, and serum bilirubin and alanine aminotransferase levels at baseline. Pearson's chi-square test was employed in the univariate analyses to compare the proportion of subjects with response to therapy within each category of potential predictors. Multivariate logistic regression was used to evaluate the independent effect of study variables on treatment response. A stepwise regression with forward selection was used. A variable had to be significant at the 0.10 level before it could enter into the model and had to be significant at the 0.15 level for it to remain in the regression model.

Survival

Patient survival was determined using the Kaplan-Meier [12] estimation with 95% confidence intervals derived from standard errors. Patients were censored at the date of last contact. Comparison of survival between the 2 treatment groups was carried out using Kaplan-Meier plots and log-rank tests [12].

Predictors of Mortality

Potential factors associated with effects on mortality were studied. The Kaplan-Meier product limit method [12] was used to compare survival in the subsets, and the Cox regression model [13] was used to assess the independent effect of the predictors on survival as well as any potential confounding of the effect of the randomized treatment. A stepwise regression with forward selection was used with a significance level of $P = .10$ being needed to enter into the model and a significance level of $P = .15$ to remain in the model. Recipient age was not included in the model because of nonproportionality, and the results were stratified by recipient age. Acute GVHD (grade III-IV) was excluded from the model because of colinearity between progressive onset and acute GVHD.

Complications After Transplantation

Complications studied included hypertension, hyperglycemia requiring treatment, constipation, somnolence, seizures, neuropathy, thrombotic thrombocytopenic purpura (TTP), avascular necrosis, and infections. Pearson's chi-square test was employed to compare the proportion of patients with complications in the 2 treatment groups.

Infections Following BMT

To account for multiple events, density incidence was used to describe the total rate of infections. Density incidence was defined as the total number of infections per 1000 patient-days. Statistical comparison of the density incidence was done by using the Mantel-Haenszel chi-square test [14] for person-days data.

RESULTS

The clinical characteristics of the 54 patients are shown in Table 1. There were 27 patients in each treatment group. Patients randomized to receive thalidomide were slightly older than those who did not receive it (median age, 44 versus 37 years; $P = .01$), but there were no significant differences in pretransplantation diagnoses, types of transplant donors, conditioning regimens, prophylaxis for acute GVHD, presence or stage of acute GVHD, or pattern of onset and organ involvement with CGVHD. Overall, 27 patients had high-risk CGVHD. Nine patients (5 receiving thalidomide and 4 receiving no thalidomide) had progressive onset of CGVHD. Six patients (3 in each group) had hyperbilirubinemia, and 22 patients (10 in the no-thal group and 12 in the thal group) had significant thrombocytopenia at the time of diagnosis of CGVHD. Eight of the 27 patients (4 in the thal group, 4 in the no-thal group) had 2 high-risk factors, whereas 3 patients (1 in the thal group, 2 in the no-thal group) had all 3 high-risk factors at diagnosis of CGVHD.

Response to Therapy

As shown in Table 2, the response to combination immunosuppressive therapy was evaluated at 2 months, 6 months, and 1 year from randomization. Of the 54 patients enrolled, the number of patients evaluable for response was 51 at 2 months, 49 at 6 months, and 42 at 1 year. Three patients in the thal group died within 1 month of starting therapy and were unevaluable. Two patients in the no-thal group relapsed and died and thus had no response assessed at 6 months and 1 year. Two additional patients in the thal group died and were not evaluable at 1 year. Five patients (2 in the thal group and 3 in the no-thal group) have not as yet completed 1 year of therapy.

Complete and partial responses were observed in 86%, 85%, and 79% of the patients at 2 months, 6 months, and 1 year, respectively. At 1 year, 22 patients (52%) had a CR. Response rates were similar in both treatment groups at all 3 time points. Clinical response rates (CR + PR) in the thal and no-thal groups were similar at 2 months (83% versus 89%, $P = .7$), 6 months (88% versus 84%, $P > .8$) and 1 year

Table 1. *Clinical Characteristics at Study Entry**

	Thal Group, n (%)	No-Thal Group, n (%)	P
Patient Demographics			
No. of patients	27 (50)	27 (50)	
Diagnosis			
Acute leukemia	12 (44)	12 (44)	.39
CML	12 (45)	11 (41)	
Other malignancies	2 (7)	3 (11)	
Nonmalignant Diseases	1 (4)	1 (4)	
Age, y			
Median (range)	44 (17-60)	37 (12-50)	.01
<20	1 (4)	5 (19)	
20-29	2 (7)	5 (19)	
30-39	7 (26)	5 (19)	
≥40	17 (63)	12 (43)	
Donor/recipient sex mismatch			
Male recipient with female donor	5 (19)	4 (15)	>.8
Others	17 (63)	19 (70)	
Donor/recipient CMV sero-status (either or both +)	17 (63)	19 (70)	.77
Type of transplant			
Sibling donor	18 (67)	16 (59)	.77
Unrelated donor	9 (33)	11 (41)	
HLA mismatch (related donor)	3 (17)	1 (6)	.60
HLA mismatch (unrelated donor)	1 (11)	4 (36)	.31
Conditioning regimens			
TBI + cyclophosphamide	25 (92)	23 (85)	.66
Others	2 (8)	4 (15)	
Prophylaxis for acute GVHD			
Methotrexate + cyclosporine	20 (74)	22 (81)	.50
T-cell depletion	5 (19)	4 (15)	
Others	2 (7)	1 (4)	
Acute GVHD			
Grade II-IV acute GVHD	18 (67)	20 (74)	.55
Grade III-IV acute GVHD	7 (26)	6 (22)	.75
Characteristics of CGVHD			
Onset of CGVHD			
De novo	6 (22)	4 (15)	>.8
Quiescent	16 (59)	19 (70)	
Progressive	5 (19)	4 (15)	
Time to treatment (days after transplant) median (range)	190 (63-794)	194 (75-812)	>.8
Organ involvement			
Skin	16 (60)	21 (78)	.14
Oral	24 (89)	21 (78)	.27
Liver	12 (44)	9 (33)	.4
Gastrointestinal	21 (78)	17 (63)	.23
Lungs	9 (33)	14 (52)	.16
Eyes	13 (48)	9 (33)	.26
High-risk CGVHD†	14 (52)	13 (48%)	.8
Standard risk	13 (48%)	14 (52%)	
Platelet count, median (range)	118 (17-352)	105 (39-384)	.8
WBC count, median (range)	5150 (2100-15,000)	3900 (1400-8400)	.18
Bilirubin ≥3 mg/dL	3 (11)	3 (11)	>.8
Alanine aminotransferase >250 units/dL	4 (15)	5 (19)	.71

*P values reflect chi square or the Fisher exact test comparisons between treatment groups. CML indicates chronic myelogenous leukemia; CMV, cytomegalovirus; TBI, total body irradiation; GVHD, graft-versus-host disease; plts, platelet count; WBC, white blood cell count.

†High-risk CGVHD was defined as presence of either progressive onset of disease, bilirubin ≥3 mg/dL or platelet count of <100,000/μL.

(85% versus 73%, $P = .5$). In patients with high-risk disease, response rates were similar over time and did not differ in the 2 treatment groups (Table 2), although a few more patients in the no-thal group had either no response or flare of CGVHD at their 6-month and 1-year evaluations.

Predictors of Response

We analyzed 13 clinical factors as potential predictors of response at 2 months and 1 year (Table 3). Similar findings were observed at 6 months (not shown). Use of thalidomide was not associated with more frequent responses. In univariate analysis, more frequent response to therapy was seen in recipients of related donor transplants and in patients with de novo/quiescent onset of CGVHD. Recipients of related donor transplant had more frequent early responses (94% versus 72%, $P = .08$). More frequent early responses were also seen in patients with de novo and quiescent onset of CGVHD (91% versus 63% at 2 months, $P = .06$ and 84% versus 40% at 1 year, $P = .05$, respectively). Involvement of the skin also identified patients with more frequent responses at 2 months and 1 year.

In the multivariate analysis (Table 4), related donor transplant (odds ratio [OR] = 11.3; $P = .03$) and de novo or quiescent onset of disease (OR = 7.7; $P = .04$) were significant predictors of more frequent early (2 months) response. A platelet count of >100,000/μL was a significant predictor of more frequent late (1 year) response (OR = 10.4; $P = .04$). Involvement of skin was an independently significant predictor of more frequent early as well as late responses (OR = 9.7, $P = .03$ and OR = 25, $P < .01$, respectively). Randomization to thalidomide had no significant impact on response to therapy at any time point.

Of note, patients with lung involvement also showed a high response. Eight of 10 patients in the thal group and 7 of 9 patients in the no-thal group showed a clinical response at 1 year.

Survival

Thalidomide therapy for CGVHD did not lead to improved survival. After a median follow-up of 22 months (range 6-58 months), it was determined that at 2 years thalidomide-treated patients had survival rates similar to those of the control cohort (Figure 1) (range, 66% and 54%, respectively, $P = .85$) with no deaths observed in surviving patients beyond 2 years. Patients with high-risk disease had an actuarial survival of 53% (range, 33%-73%) 1 year after transplantation and 44% (range, 21%-67%) 2 years after transplantation. Therapy with thalidomide did not alter survival time in the higher-risk subgroup (2-year survival rate of 26% versus 28%, respectively, in the high-risk thal and no-thal groups, respectively, $P = .5$).

Overall, 19 patients died, 10 in the no-thal group and 9 in the thal group ($P = .8$). Three patients in the thal group died within 1 month of starting therapy because of infectious complications. Four patients in the thal group and 8 patients in the no-thal group died with severe unresponsive CGVHD. Two patients relapsed, both in the no-thal group. One patient in the thal group developed progressive multifocal leukoencephalopathy and 1 other patient in the thal group with severe continuing pancytopenia died of bacterial and fungal infections after 1 year of therapy.

Table 2. *Patient Evaluability and Frequency of Response to Therapy**

	2-Month Follow-up			6-Month Follow-up			1-Year Follow-up		
	Thal	No-Thal	*P*	Thal	No-Thal	*P*	Thal	No-Thal	*P*
All patients									
Evaluable patients	24	27		24	25		20	22	
CR, n (%)	2 (8)	2 (7)		4 (17)	7 (28)		10 (50)	12 (55)	
PR, n (%)	18 (75)	22 (81)		17 (71)	14 (56)		7 (35)	4 (18)	
CR+PR, n (%)	20 (83)	24 (89)	.7	21 (88)	21 (84)	>.8	17 (85)	16 (73)	.5
NR+Flare, n (%)	4 (17)	3 (11)		3 (12)	4 (16)		3 (15)	6 (27)	
High-risk CGVHD patients									
Evaluable patients	11	13		11	12		8	9	
CR, n (%)	1 (9)	1 (8)		2 (18)	1 (8)		3 (38)	3 (33)	
PR, n (%)	8 (73)	9 (69)		8 (73)	7 (59)		4 (50)	1 (11)	
CR+PR, n (%)	9 (82)	10 (77)	>.8	10 (91)	8 (67)	.3	7 (88)	4 (44)	.1
NR+Flare, n (%)	2 (18)	3 (23)		1 (9)	4 (33)		1 (12)	5 (56)	

**P* value represents Pearson's chi-square comparisons between patients with CR+PR versus NR+Flare at 2 months, 6 months, and 1 year. CR indicates complete response; PR, partial response; NR, no response; CGVHD, chronic graft-versus-host disease.

Table 3. *Predictors of Response: Univariate Analysis**

	2-Month Follow-up			1-Year Follow-up		
Predictor	No. of Evaluable Patients	Responders, %	*P*	No. of Evaluable Patients	Responders, %	*P*
All patients	51	86		42	79	
Treatment group						
Thalidomide	24	83	.7	20	85	.4
No thalidomide	27	89		22	73	
Age						
≥30 years	38	89	.4	30	80	.7
<30 years	13	77		12	75	
Sex mismatch						
Male recipient:female donor	7	100	.5	6	50	.1†
Others	44	84		36	83	
Type of Transplant						
Unrelated donor	18	72	.08	15	67	.2
Related donor	33	94		27	85	
Acute GVHD						
Grade III-IV	12	75	.3	9	67	.4
Grade 0-II	39	90		33	82	
Onset						
Progressive	8	63	.06	5	40	.05†
Denovo + quiescent	43	91		37	84	
Organ involvement with CGVHD						
Skin	34	94	.03	27	93	<.01†
None	17	71		15	53	
Oral	43	91	.2	37	81	.3
None	8	75		5	60	
Eye	22	91	.7	18	78	>.8
None	29	83		24	79	
Lungs	21	86	>.8	19	79	>.8
None	30	87		23	78	
Gastrointestinal	37	86	>.8	28	75	.7
None	14	86		14	86	
Liver	21	81	.4	16	75	.7
None	30	90		26	81	
Platelets <100,000/μL	19	79	.4	13	62	.1†
Platelets ≥ 100,000/μL	32	91		29	86	
Bilirubin ≥3 mg/dL	5	60	.13	4	50	.1†
Bilirubin <3 mg/dL	46	89		38	82	

*Response refers to CR or PR at the time period shown. *P* values reflect chi-square tests of significance. GVHD indicates graft-versus-host disease; CGVHD, chronic GVHD.

†Value was entered into subsequent multivariate analysis.

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