

A Survey of Diagnosis, Management, and Grading of Chronic GVHD

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ABSTRACT

Chronic GVHD (cGVHD) is a potentially devastating late complication of allogeneic stem cell transplantation. To better understand current diagnostic and treatment practices regarding this complication, we mailed a self-administered survey to 188 adult and pediatric transplantation programs. The survey collected data on experience with therapies for cGVHD and presented 6 vignettes to assess agreement about the diagnosis, clinical management, grading, and prognosis of patients with symptoms of cGVHD. Response rate to the survey was 51%. Of the respondents, 28% felt they had "great success" in treating patients with systemic corticosteroids, and 13% had similar success with cyclosporine or mycophenolate mofetil; less success and experience were reported with other agents. Respondents estimated an average 3-year, nonrelapse mortality of 16% (95% CI, 14%-19%) for patients assessed to have limited disease and 39% (95% CI, 36%-43%) for extensive disease. Analysis of responses to the 6 vignettes showed that agreement was greatest for supportive care issues, willingness to enroll patients in clinical trials, and use of systemic immunosuppression for symptomatic cGVHD. Less agreement was seen for diagnosis and management when cGVHD manifestations were atypical or less severe, the decision of whether to taper immunosuppression in the face of stable symptoms, and for assignment of mild, moderate, or severe cGVHD grades. Most respondents were willing to use systemic immunosuppression to treat symptoms that they believed to be caused by cGVHD, but differences of opinion about cGVHD diagnosis and disease activity resulted in significant practice variation. Low estimates of treatment success were noted and reflected an overall pessimism about the success of therapy for cGVHD. We conclude that studies defining appropriate diagnostic pathways, criteria for disease activity, and prognosis could help standardize management of cGVHD. There is an urgent need to develop and test new approaches to treat cGVHD.

KEY WORDS

Chronic graft-versus-host disease • Allogeneic stem cell transplantation

INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a serious late complication of allogeneic transplantation because of its influence on health, relapse, and survival [1-8]. Large observational studies identify cGVHD as the leading cause of nonrelapse deaths occurring more than 2 years posttransplantation [8]. However, it is difficult to determine optimal management strategies or to test new strategies, because of the great variability in organ involvement and the waxing and waning natural history of cGVHD. Systemic immunosuppression is the basis of treatment, yet there is a delicate balance between controlling cGVHD symptoms and

increasing susceptibility to infections, a major cause of death in these patients. Central to managing cGVHD is the ability to (1) recognize its initial manifestations and establish the diagnosis; (2) assess its severity, trajectory, and response to therapy; and (3) appreciate its impact on survival and quality of life. A 1989 survey of transplantation physicians showed moderate levels of agreement about cGVHD diagnosis and management [9]. We undertook a similar survey to provide an updated cross-sectional view of current practices.

A 6-page survey covering diagnosis, treatment, and management of cGVHD was designed, pilot tested, and mailed to US transplantation centers. The survey also

included 6 vignettes in which respondents were asked to grade cGVHD severity and to provide an estimate of 3-year nonrelapse mortality. Results from this survey allow comment on areas of agreement and controversy and identify areas for future work.

MATERIALS AND METHODS

Survey Development

All authors contributed to the design of the survey instrument, which was modeled after a similar study published in 1989 by Atkinson et al. [9]. The survey asked about the use of therapeutic agents to manage cGVHD and the perceived success of these interventions. Four response categories were offered: “No, I have not used this agent” and “Yes, I have used this agent with (1) no, (2) some, or (3) great success.” A separate section presented 9 clinical management problems (persistent erythema, pruritis, mouth sores, keratoconjunctivitis, chronic diarrhea, joint contractures, vaginal strictures, bronchiolitis obliterans, and scleroderma) and asked about any locally developed or novel therapies. Six vignettes were presented to span the spectrum of cGVHD diagnosis, management, and severity assessment, and respondents were asked to estimate 3-year nonrelapse mortality for each case. Finally, center and practitioner information was collected. Pilot testing was performed to assess comprehension and clarity. The clinical vignettes and questions are reproduced in the Appendix.

Data Collection

The survey was initially mailed to centers in the United States that participate in the International Bone Marrow Transplant Registry (IBMTR) and the Pediatric Blood and Marrow Transplant Consortium. A drawing for a cash prize was used as an incentive to encourage participation. Nonrespondents received 2 e-mailed reminders and another copy of the survey (attached electronically). Participants were surveyed between December 2000 and February 2001.

Biostatistical Analysis

Descriptive statistics are reported for center characteristics, use of therapies and their perceived benefits, and responses to vignettes. Vignette items were classified into 1 of 5 categories: clinical diagnosis (7 questions), use of diagnostic tests (6 questions), clinical management (22 questions), grading and prognosis (18 questions), and supportive care (7 questions including referral to specialists, prophylactic antibiotics, and immunizations). When answers were dichotomous, the degree of agreement was quantified among respondents by calculating the percentage agreeing. We interpreted degree of agreement in the following way: 50% to 60% = disagreement (-), because this level is no better than chance; 61% to 70% = low agreement (+); 71% to 80% = moderate agreement (++); 81% to 90% = strong agreement (+++); and $\geq 91\%$ = very strong agreement (++++). Practitioners were divided into higher volume (caring for at least 10 patients with cGVHD) and lower volume and primarily adult versus pediatric practices. Levels of agreement were compared among these groups.

Associations between assessed severity of cGVHD and nonrelapse mortality estimates were calculated for each

vignette separately, then summarized across vignettes and respondents. The pooled estimates were calculated by generating 1 estimate per respondent for each severity category (limited, extensive, mild, moderate, and severe cGVHD) based on vignette responses and then calculating the mean across the population.

RESULTS

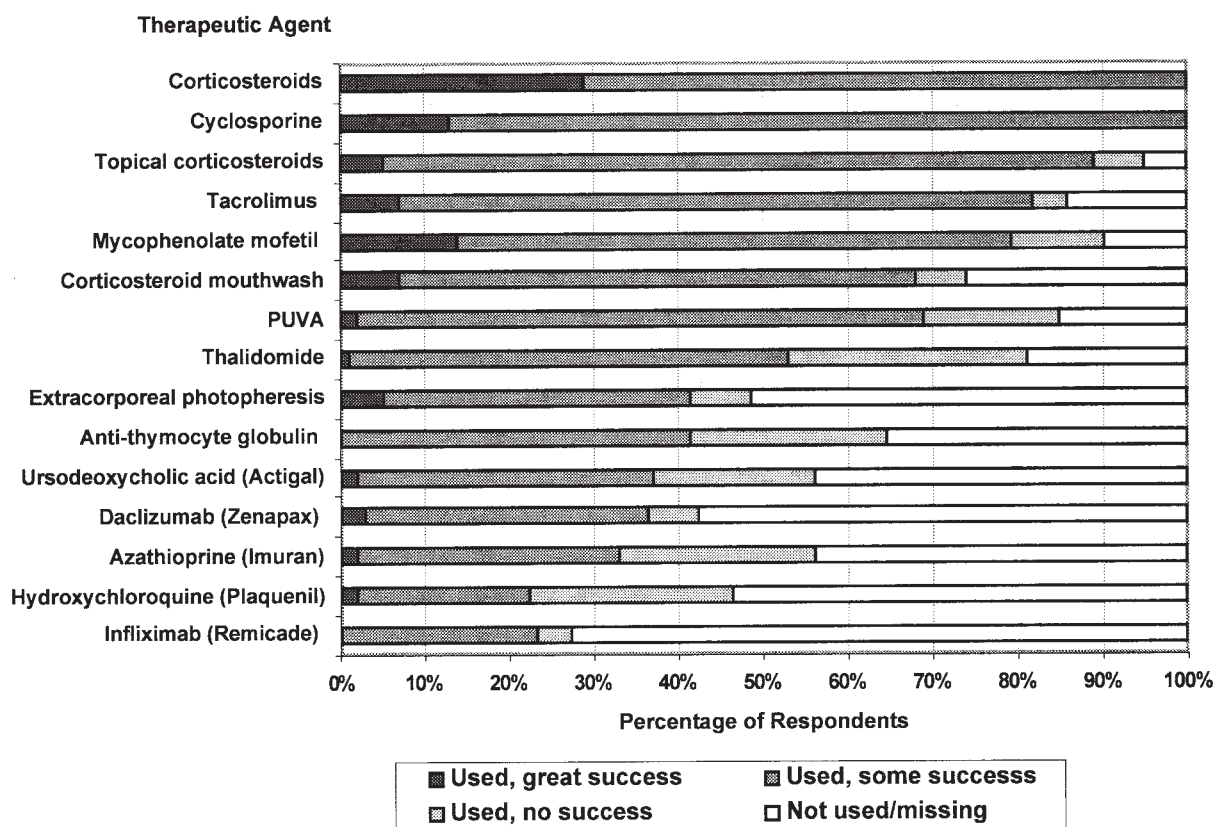
Center Demographics

A total of 220 surveys were mailed to centers. Of these surveys, 32 were subsequently deemed to be ineligible (centers performed autologous procedures only, mailings sent to different individuals practicing at the same center, or institution no longer performing transplantation procedures). Among the eligible institutions, there were 94 responders (50%) with evaluable surveys, 2 responders (1%) with unevaluable surveys, and 92 nonresponders (49%). The median number of allogeneic procedures performed annually at each respondent center was 30, and the median number of patients with cGVHD cared for by each center was estimated at 20. Respondents estimated that they personally took care of a median of 10 patients with cGVHD. Multiple methods of GVHD prophylaxis were used at centers, including cyclosporine (94%), tacrolimus (61% of centers), standard methotrexate (76%), mini-methotrexate (41%), and T-cell depletion (46%). Only 18% of centers reported having research protocols to treat cGVHD, and 7% had studies to prevent cGVHD. Of the respondents, 93% stated that they would be interested in participating in a group dedicated to multicenter studies of cGVHD, such as evaluating new grading schemes, management strategies, new drugs or combinations of drugs, or collecting serum or tissue samples.

There was no evidence for systematically different responses from higher volume versus lower volume or adult versus pediatric practices, and responses were combined for analysis.

Diagnosis of cGVHD

Agreement about the clinical diagnosis and use of biopsies to diagnose cGVHD was moderate, with 79% average agreement (range, 54%-96%) for the 7 questions regarding clinical diagnosis and 76% (range, 60%-93%) for the 6 questions about use of diagnostic tests. There was very strong agreement that a persistent confluent rash present on day 120 was cGVHD (item 1.4, 91% agreement) and that bilateral buccal ulcers with negative herpes simplex virus (HSV) culture results in month 14 was cGVHD (item 1.8, 96%). Most respondents agreed that a patient presenting on day 190 with pruritis, eosinophilia, and thrombocytopenia had cGVHD (item 6.1, 80%). In contrast, there was disagreement about whether an isolated elevated alkaline phosphatase level on day 160 posttransplantation was cGVHD (item 5.2, 54%). Agreement about use of diagnostic tests varied. There was very strong agreement about performing a bronchoalveolar lavage on day 140 posttransplantation for dyspnea on exertion with interstitial infiltrates and negative sputum culture results (item 3.3, 93%) and about performing a skin biopsy on day 140 for an isolated rash involving the arms, chest, upper back, and thighs (item 4.1, 89%). However, there was low agreement on whether a liver



Experience and perceived success with the 15 most common therapies for cGVHD.

biopsy should be performed on day 180 posttransplantation for an isolated direct hyperbilirubinemia with normal ultrasound (item 1.5, 60%).

Management of cGVHD

Corticosteroids (systemic and topical), cyclosporine, tacrolimus, mycophenolate mofetil, psoralen and UV-A (PUVA), thalidomide, antithymocyte globulin, extracorporeal photopheresis, ursodeoxycholic acid, daclizumab, azathioprine, hydroxychloroquine, and infliximab had some or great success by 20% or more of respondents. However, of these agents, only systemic corticosteroids, cyclosporine, and mycophenolate mofetil were deemed of “great success” by more than 10% of the respondents (Figure).

Suggestions for managing persistent erythema, pruritis, mouth ulcers, keratoconjunctivitis, chronic diarrhea, joint contractures, vaginal strictures, bronchiolitis obliterans, and scleroderma were solicited, and the list of responses is available from the authors. In general, answers could be divided into recommendations for specific systemic immunosuppressive agents, supportive care (including nutrition, massage, physical therapy, and assistive devices), local therapies, and infection-preventive strategies.

The 22 items from the vignettes considered to measure management of cGVHD showed moderate agreement (mean, 76%; range, 53%-97%). Very strong agreement was found for enrolling patients in phase I, II, and III clinical trials of therapy for cGVHD, except in cases of asymptomatic cGVHD (item 5.4, 65%) or atypical manifestations

(item 6.5, 53%). There was also very strong agreement for increasing or starting immunosuppressive therapy for a confluent rash involving the chest and back on day 160 with associated thrombocytopenia (item 4.4, 91%), for severe sclerodermatous changes of the lower extremity (item 2.5, 96%), and for symptomatic interstitial infiltrates once infection was ruled out (item 3.5, 97%). Most respondents would also use systemic immunosuppression to treat dry eyes and mouth and oral lichen planus at 9 months (item 2.3, 85%). Most respondents would taper systemic immunosuppression if a biopsy-proven lichenoid skin rash had resolved after 2 weeks of steroid therapy (item 5.1, 86%) but would not taper immunosuppression 3 months after interstitial pneumonitis if a patient was still symptomatic (item 3.6, 82%).

Areas of less agreement about cGVHD management were identified and could be categorized as: (1) disagreement about cGVHD diagnosis (with high correlation between diagnosis of cGVHD and decision to start or increase systemic treatment); (2) use of topical therapies, such as corticosteroids or PUVA; and (3) whether to taper medications when cGVHD manifestations were stable. Specifically, there was low agreement about the need for increased immunosuppression for isolated oral lichen planus on day 70 (item 3.2, 53%), the usefulness of topical steroids (item 4.3, 58%) or PUVA for confluent erythema in the setting of thrombocytopenia (item 4.5, 61%), and the decision to taper steroids with unchanged sclerodermatous manifestations after 3 months (item 2.8, 68%) or with increasing alkaline phosphatase level as an isolated finding (item 5.3, 61%).

Estimates of cGVHD Severity and Prognosis*

Vignette No.	Grade	Percentage or No. of Respondents	3-Year Nonrelapse Mortality, Mean, % (95% CI)		Grade	Percentage or No. of Respondents	3-Year Nonrelapse Mortality, Mean, % (95% CI)	
1	Limited	28%	14 (10-19)		Mild	20%	15 (9-22)	
	Extensive	72%	30 (26-33)		Moderate	74%	28 (24-31)	
2	Limited	15%	23 (14-32)		Severe	6%	52 (35-69)	
	Extensive	85%	35 (31-39)		Mild	2%	16 (0-64)	
					Moderate	46%	30 (25-35)	
3	Limited	15%	50 (33-66)		Severe	52%	38 (33-44)	
	Extensive	85%	48 (44-53)		Mild	—	—	
					Moderate	29%	33 (26-41)	
4	Limited	8%	29 (4-53)		Severe	71%	54 (49-59)	
	Extensive	92%	45 (40-49)		Mild	—	—	
					Moderate	36%	31 (25-37)	
5	Limited	86%	12 (10-13)		Severe	64%	51 (46-57)	
	Extensive	14%	21 (13-28)		Mild	74%	11 (9-13)	
					Moderate	26%	18 (13-23)	
6	Limited	28%	16 (11-22)		Severe	—	—	
	Extensive	72%	37 (31-42)		Mild	8%	17 (7-26)	
					Moderate	49%	22 (18-26)	
Summary	Limited	76	16 (14-19)		Severe	43%	45 (37-53)	
	Extensive	87	39 (36-43)		Mild	65	12 (10-14)	
					Moderate	85	28 (25-31)	
				Severe	76	48 (44-52)		

*Percentage of respondents selecting each severity category (limited/extensive and mild/moderate/severe) for the 6 vignettes, and the mean 3-year, nonrelapse mortality estimate. Summary statistics are pooled across respondents and vignettes.

Stratification of management decisions by diagnostic impressions showed that once cGVHD was believed to be present, respondents were willing to treat aggressively with systemic immunosuppression. In general, there was no evidence that respondents were willing to tolerate some manifestations to spare patients from further immunosuppression. The 1 exception was mouth ulcers, fatigue, and weight loss at month 14 (item 1.9, 64%), for which most respondents agreed that the patient had cGVHD, but many would not treat systemically.

Supportive Care

There was a generally high level of agreement about appropriate supportive care for patients with cGVHD (88%; range, 78%-98%). Respondents were likely to vaccinate patients when appropriate (item 5.5, 88%); avoid vaccination with live viruses, such as measles, mumps, rubella (MMR) (item 4.8, 98%); prescribe penicillin (item 2.4, 89%) and pneumocystosis prophylaxis (item 2.7, 96%); and refer to specialists (item 2.2, 93%). There was only moderate agreement about tetanus vaccination at day 360 (item 4.7, 78%).

Assessment of Severity and Survival

Agreement about limited and extensive grading was reasonably good for the 6 vignettes (82%; range, 72%-92%), but agreement according to mild, moderate, and severe grading was not as good (Table). On average, respondents estimated a 3-year nonrelapse mortality of 16% (95% CI, 14%-19%) for patients with limited disease and 39% (95% CI, 36%-43%) for those with extensive disease. For patients classified as having mild, moderate, or severe cGVHD, the estimates were 12% (95% CI, 10%-14%), 28% (95% CI, 25%-31%), and 48% (95% CI, 44%-52%), respectively.

DISCUSSION

We report the results of a mailed survey sent to adult and pediatric transplantation centers participating in the IBMTR or the Pediatric Blood and Marrow Transplant Consortium. Agreement was highest for supportive care measures, assignment of limited/extensive grades, and management with immunosuppression when the diagnosis of cGVHD was felt to be clear and the manifestations severe. Areas of low-to-moderate agreement, or even frank disagreement, were identified in situations in which the presentation of cGVHD was atypical, manifestations were less severe, or stable functional limitations persisted, similar to the findings of Atkinson and colleagues [9]. In these circumstances, the presence or absence of cGVHD was a major source of disagreement, and the decision to treat correlated significantly with a diagnosis of cGVHD. Because cGVHD can often be definitively diagnosed on biopsy, our findings support the use of biopsy as a routine diagnostic procedure in the evaluation of cGVHD.

Although we hypothesized that practice variation might result from decisions to treat certain manifestations less aggressively because of concern about increasing susceptibility to infections, we found that most respondents were willing to treat with systemic immunosuppression if they believed cGVHD was present. The sole exception was oral ulcers, fatigue, and weight loss in month 14. Although many respondents identified this group of symptoms as cGVHD, fewer indicated that they would start systemic immunosuppressive therapy based on these symptoms.

Although respondents did not have high agreement on whether patients presented in the vignettes had mild, moderate, or severe cGVHD, remarkably consistent estimates of 3-year nonrelapse mortality were associated with each severity grading. Pooled estimates of 3-year nonrelapse mortality

ranged from 12% for patients assessed with mild disease to 48% for those thought to have severe disease. These estimates were actually very similar to survival data from a retrospective study by the IBMTR and the National Marrow Donor Program (S.J.L., unpublished data, 2001). The high mortality associated with cGVHD supports aggressive clinical research efforts in this area. Of the respondents to our survey, 93% expressed interest in participating in multicenter studies of grading schemes, management strategies, and new drugs or combinations of drugs, a result consistent with our impression that the transplantation community recognizes a need to study ways of improving therapy for cGVHD.

The major limitations of our study were the data collection mechanism (a mailed survey to US transplantation centers only) and the 50% response rate (despite 3 attempts to contact physicians and offering an incentive to participate). Thus our observations are based on a self-selected subset of transplantation programs and may not adequately summarize current practice in the United States. Also, clinical decisions were assessed using a series of vignettes, which may not recapitulate actual practice. Nevertheless, our results suggest that a major source of practice variation may reflect different thresholds for diagnosing cGVHD and variation in

assessments of disease severity and trajectory. Respondents generally followed the tenet of aggressive systemic immunosuppression if they believed cGVHD to be active. Future studies to standardize the diagnosis and grading of cGVHD and to develop better therapy for cGVHD are needed.

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APPENDIX

The following 6 vignettes were developed to represent common, and often difficult, clinical scenarios. Please read each case carefully, then indicate your choices by circling 1 answer for each question. Unless otherwise noted, “systemic immunosuppression” refers to corticosteroids, cyclosporine, tacrolimus, mycophenolate mofetil, rapamycin, or azathioprine.

Vignette 1: 35-year-old man, underwent matched-unrelated BMT for CML, methotrexate/cyclosporine*

Day 12: Febrile neutropenia, started β -lactam and aminoglycoside
Day 18: Engraftment
Day 21: Macular-papular rash involving 18% of body, antibiotics changed
Day 23: Progression of rash to involve 54% of body surface
Day 120: Persistent confluent erythema
Day 180: Feels well, no rash, total bilirubin 5.4, direct 4.4, right upper quadrant ultrasound normal
Month 14: Feels tired, no rash, normal bilirubin, bilateral buccal mouth ulcers noted, HSV culture negative, 2-kg weight loss over 1 month

		No	Yes	Agreement	
I.1	I would perform a skin biopsy on day 21	30	61	0.67	+
I.2	I would start steroids on day 21	69	20	0.78	++
I.3	I would start steroids on day 23	12	76	0.87	+++
I.4	This patient had cutaneous cGVHD day 120	7	77	0.91	++++
I.5	I would perform a liver biopsy on day 180	34	53	0.60	+
I.6	This patient had hepatic cGVHD on day 180	19	64	0.76	++
I.7	I would start or increase systemic immunosuppression on day 180	24	62	0.72	++
I.8	This patient had oral cGVHD in month 14	5	83	0.96	++++
I.9	I would start or increase systemic immunosuppression in month 14	28	52	0.64	+
I.10	Maximum grade of cGVHD	None (0%) Limited (28%) Extensive (72%)		0.72	++
I.11	Maximum severity of cGVHD	None (0%) Mild (20%) Moderate (74%) Severe (6%)			
I.12	Estimated nonrelapse mortality within the next 3 years	20% (5%-75%), mean 26% (n = 86)			

*Numbers for maximum grade and severity of GVHD and for the estimated 3-year nonrelapse mortality may not add up to 100% because of rounding.

Vignette 2: 22-year-old man with aplastic anemia, underwent matched-sibling BMT, methotrexate/cyclosporine***Day 20:** Engraftment**Month 9:** Dry eyes and mouth, oral lichen planus**Month 13:** Severe sclerodermatous changes and loss of hair on lower extremities**Month 16:** Scleroderma unchanged

	No	Yes	Agreement		
2.1	I would perform a Schirmer's test at 9 months	26	64	0.73	++
2.2	I would refer this patient to an ophthalmologist at 9 months	6	84	0.93	++++
2.3	I would start or increase systemic immunosuppression at 9 months	14	77	0.85	+++
2.4	I would start or continue penicillin prophylaxis at 9 months	9	83	0.89	+++
2.5	I would start or increase systemic immunosuppression at 13 months	4	87	0.96	++++
2.6	I would be willing to enroll this patient in a Phase II clinical trial of a novel immunosuppressive medication at month 13	6	84	0.93	++++
2.7	I would start or continue pneumocystis pneumonia prophylaxis at 13 months	4	85	0.96	++++
2.8	I would taper systemic immunosuppression at month 16	57	29	0.68	+
2.9	Maximum grade of cGVHD	None (0%) Limited (14%) Extensive (86%)		0.86	+++
2.10	Maximum severity of cGVHD	None (0%) Mild (2%) Moderate (48%) Severe (50%)			
2.11	Estimated nonrelapse mortality within the next 3 years	30% (2.5%-95%), mean 33% (n = 86)			

*Numbers for maximum grade and severity of GVHD and for the estimated 3-year nonrelapse mortality may not add up to 100% because of rounding.

Vignette 3: 46-year-old woman with AML in second remission, underwent mismatched-related BMT from daughter, methotrexate/tacrolimus, patient and donor CMV negative***Day 24:** Engraftment**Day 45:** Acute GVHD, resolved with steroids, taper in progress**Day 70:** Oral lichen planus**Day 140:** Dyspnea on exertion, chest x-ray and computed tomography showed interstitial infiltrates, sputum cultures negative**Day 240:** Unable to do strenuous tasks, pulmonary function tests show an FEV₁ of 40%**Day 380:** Stable clinical status, pulmonary function tests show an FEV₁ of 42%

	No	Yes	Agreement		
3.1	This patient had cGVHD on day 70	21	71	0.77	++
3.2	I would start or increase systemic immunosuppression on day 70	43	47	0.53	-
3.3	I would perform a bronchoalveolar lavage on day 140	6	85	0.93	++++
3.4	I would perform a transbronchial biopsy on day 140	22	66	0.74	++
3.5	I would start or increase systemic immunosuppression on day 142 if cultures for infectious organisms are negative	3	88	0.97	++++
3.6	I would taper systemic immunosuppression on day 240	73	16	0.82	+++
3.7	I would be willing to enroll this patient in a Phase I clinical trial of a novel immunosuppressive medication on day 240	8	83	0.92	++++
3.8	I would taper systemic immunosuppression on day 380	24	65	0.73	++
3.9	Maximum grade of cGVHD	None (2%) Limited (16%) Extensive (81%)		0.83	+++
3.10	Maximum severity of cGVHD	None (0%) Mild (0%) Moderate (30%) Severe (70%)			
3.11	Estimated nonrelapse mortality within the next 3 years	50% (10%-95%), mean 48% (n = 86)			

*Numbers for maximum grade and severity of GVHD and for the estimated 3-year nonrelapse mortality may not add up to 100% because of rounding.

Vignette 4: 50-year-old woman, underwent matched-sibling peripheral blood transplantation for refractory anemia with excess blasts, methotrexate/tacrolimus*

Day 16: Engraftment
Day 30: Acute GVHD of skin, resolved with steroids
Day 140: Feels well, macular-papular pruritic rash involving arms, chest, upper back, upper thighs
Day 160: Confluent erythema involving the chest and back, platelets 80,000/ μ L
Day 360: Confluent erythema over chest and back, chronic diarrhea, 10-kg weight loss

		No	Yes	Agreement	
4.1	I would perform a skin biopsy on day 140	9	82	0.89	++++
4.2	I would start or increase systemic immunosuppression on day 140	22	68	0.77	++
4.3	I would prescribe topical steroids on day 140	35	53	0.58	+
4.4	I would start or increase systemic immunosuppression on day 160	9	81	0.91	++++
4.5	I would prescribe PUVA on day 160	52	36	0.61	+
4.6	I would be willing to enroll this patient in a Phase III clinical trial of standard versus more intensive immunosuppression on day 160	4	87	0.97	++++
4.7	I would administer the tetanus vaccine on day 360	69	21	0.78	++
4.8	I would administer the measles, mumps, rubella vaccine on day 360	88	2	0.98	++++
4.9	Maximum grade of cGVHD	None (0%) Limited (8%) Extensive (92%)		0.92	++++
4.10	Maximum severity of cGVHD	None (0%) Mild (1%) Moderate (37%) Severe (62%)			
4.11	Estimated nonrelapse mortality within the next 3 years	40% (5%-95%), mean 43% (n = 88)			

*Numbers for maximum grade and severity of GVHD and for the estimated 3-year nonrelapse mortality may not add up to 100% because of rounding.

Vignette 5: 21-year-old woman, Philadelphia chromosome-positive ALL, underwent matched-sibling BMT, mini-methotrexate/tacrolimus*

Day 14: Engraftment
Day 130: Macular-papular rash on back, biopsy showed lichenoid cGVHD
Day 144: Rash resolved on 1 mg/kg steroids
Day 160: Elevation of alkaline phosphatase, 2 \times normal, otherwise well
Day 174: Elevation of alkaline phosphatase, 3 \times normal, otherwise well
Day 365: Returned to school

		No	Yes	Agreement	
5.1	I would taper steroids on day 144	13	78	0.86	+++
5.2	This patient had liver cGVHD on day 160	40	42	0.54	-
5.3	I would taper steroids on day 174	54	35	0.61	+
5.4	I would be willing to enroll this patient in a phase II clinical trial of a novel immunosuppressive medication on day 174	58	32	0.65	+
5.5	I would administer the influenza vaccine on day 365	12	79	0.88	+++
5.6	I would administer the measles, mumps, rubella vaccine on day 365	70	19	0.79	++
5.7	Maximum grade of cGVHD	None (4%) Limited (83%) Extensive (13%)		0.86	+++
5.8	Maximum severity of cGVHD	None (4%) Mild (72%) Moderate (24%) Severe (0%)			
5.9	Estimated nonrelapse mortality within the next 3 years	10% (2.5%-50%), mean 13% (n = 83)			

*Numbers for maximum grade and severity of GVHD and for the estimated 3-year nonrelapse mortality may not add up to 100% because of rounding.

Vignette 6: 5-year-old boy with AML in second remission, underwent transplantation from matched sibling, methotrexate/cyclosporine*

Day 19:	Engrafted
Day 25:	Acute GVHD of skin, resolved on steroids
Day 180:	Steroids and cyclosporine discontinued
Day 190:	Pruritis, eosinophilia, platelets 75,000/μL
Day 200:	Presented with chest pain, dyspnea on exertion, echocardiogram showed large pericardial effusion, pericardiocentesis showed transudative fluid, cultures, and cytology negative
Day 210:	Pericardial fluid reaccumulated, pericardial window placed, no further symptoms

		No	Yes	Agreement	
6.1	This patient had cGVHD on day 190	17	72	0.80	+++
6.2	I would start or increase systemic immunosuppression on day 190	21	67	0.75	++
6.3	This patient had cGVHD on day 200	18	66	0.78	++
6.4	I would start or increase systemic immunosuppression on day 200	25	60	0.70	++
6.5	I would be willing to enroll this patient in a Phase II clinical trial of a novel immunosuppressive medication on day 200	39	47	0.53	-
6.6	Maximum grade of cGVHD	None (15%) Limited (23%) Extensive (62%)		0.73	++
6.7	Maximum severity of cGVHD	None (12%) Mild (7%) Moderate (44%) Severe (37%)			
6.8	Estimated nonrelapse mortality within the next 3 years	25% (5%-80%), mean 31% (n = 70)			

*Numbers for maximum grade and severity of GVHD and for the estimated 3-year nonrelapse mortality may not add up to 100% because of rounding.

REFERENCES

- Sullivan KM, Witherspoon RP, Storb R, et al. Alternating-day cyclosporine and prednisone for treatment of high-risk chronic graft-v-host disease. *Blood*. 1988;72:555-561.
- Sullivan KM, Witherspoon RP, Storb R, et al. Prednisone and azathioprine compared with prednisone and placebo for treatment of chronic graft-v-host disease: prognostic influence of prolonged thrombocytopenia after allogeneic marrow transplantation. *Blood*. 1988;72:546-554.
- Wingard JR, Piantadosi S, Vogelsang GB, et al. Predictors of death from chronic graft-versus-host disease after bone marrow transplantation. *Blood*. 1989;74:1428-1435.
- Loughran TP Jr, Sullivan K, Morton T, et al. Value of day 100 screening studies for predicting the development of chronic graft-versus-host disease after allogeneic bone marrow transplantation. *Blood*. 1990;76:228-234.
- Syrjala KL, Chapko MK, Vitaliano PP, Cummings C, Sullivan KM. Recovery after allogeneic marrow transplantation: prospective study of predictors of long-term physical and psychosocial functioning. *Bone Marrow Transplant*. 1993;11:319-327.
- Sutherland HJ, Fyles GM, Adams G, et al. Quality of life following bone marrow transplantation: a comparison of patient reports with population norms. *Bone Marrow Transplant*. 1997;19:1129-1136.
- Duell T, van Lint MT, Ljungman P, et al. Health and functional status of long-term survivors of bone marrow transplantation. EBMT Working Party on Late Effects and EULEP Study Group on Late Effects. European Group for Blood and Marrow Transplantation. *Ann Intern Med*. 1997;126:184-192.
- Socie G, Stone JV, Wingard JR, et al. Long-term survival and late deaths after allogeneic bone marrow transplantation. Late Effects Working Committee of the International Bone Marrow Transplant Registry. *N Engl J Med*. 1999;341:14-21.
- Atkinson K, Horowitz MM, Gale RP, Lee MB, Rimm AA, Bortin MM. Consensus among bone marrow transplanters for diagnosis, grading and treatment of chronic graft-versus-host disease. Committee of the International Bone Marrow Transplant Registry. *Bone Marrow Transplant*. 1989;4:247-254.