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Analysis of Gastrointestinal and Hepatic Chronic Grant-versus-Host Disease Manifestations on Major Outcomes: A Chronic Grant-versus-Host Disease Consortium Study

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A B S T R A C T

Although data support adverse prognosis of overlap subtype of chronic grant-versus-host disease (GVHD), the importance of site of gastrointestinal (GI) and type of hepatic involvement is not known. Using data from the Chronic GVHD Consortium observational cohort study (N = 567, total of 2115 visits), we examined whether the site of GI (esophageal, upper GI, or lower GI) and type of hepatic (bilirubin, alkaline phosphatase, alanine aminotransferase) involvement are associated with overall survival (OS) and nonrelapse mortality (NRM), symptoms, quality of life (QOL) and functional status measures. In multivariate analysis utilizing data from enrollment visits only, lower GI involvement (HR, 1.67; $P = .05$) and elevated bilirubin (HR, 2.46; $P = .001$) were associated with OS; both were also associated with NRM. In multivariable analysis using all visits (time-dependent covariates), GI score greater than zero (HR, 1.69; $P = .02$) and elevated bilirubin (HR, 3.73; $P < .001$) were associated with OS; results were similar for NRM. Any esophageal involvement and GI score greater than zero were associated with both symptoms and QOL, whereas elevated bilirubin was associated with QOL. We found no consistent evidence that upper GI involvement, alkaline phosphatase, alanine aminotransferase, or NIH liver score add prognostic value for survival, overall symptom burden, or QOL. These data support important differences in patient-reported outcomes according to GI and hepatic involvement among chronic GVHD-affected patients and identify those with elevated bilirubin or higher GI score at any time, or lower GI involvement at cohort enrollment, as patients at greater risk for mortality under current treatment approaches.

INTRODUCTION

Chronic graft-versus-host disease (GVHD) is a significant source of morbidity, mortality, impaired patient-reported quality of life (QOL), greater symptom burden, and prolonged duration of immune suppressive therapy following allogeneic hematopoietic cell transplantation (HCT) [1-10]. Many [11,12], but not all retrospective studies [13,14] and prospective data from the Chronic GVHD Consortium [15], have demonstrated that overlap subtype of chronic GVHD, defined as chronic GVHD together with concurrent acute GVHD manifestations [16], is associated with worse prognosis and inferior patient-reported outcomes.

The proposed NIH Consensus criteria for organ-specific severity grading do not distinguish between the site of gastrointestinal (GI) or hepatic involvement but rather assign severity according to degree of weight loss or by magnitude of elevation of hepatic laboratory tests over the upper limit of normal, respectively. The impact on major outcomes of each site of gastrointestinal (esophagus, upper, and lower GI) or type of hepatic (transaminases, bilirubin, and alkaline phosphatase) manifestation of chronic GVHD is unknown.

We analyzed prospectively acquired observational cohort data to examine whether the site of GI involvement and type of hepatic laboratory test abnormality among patients with chronic GVHD are associated with major clinical outcomes, such as mortality, symptom burden, QOL, and functional ability.

METHODS

Chronic GVHD Observational Cohort

The Chronic GVHD Consortium is a multicenter observational cohort study of chronic GVHD-affected HCT recipients. The rationale and design of this cohort study have been previously described [17]. In brief, included are allogeneic HCT recipients age 2 or older with chronic GVHD requiring systemic immunosuppressive therapy, both those with classic chronic GVHD and those with overlap subtype [16]. Cases are classified as incident (enrollment less than 3 months after chronic GVHD diagnosis) or prevalent (enrollment 3 or more months but less than 3 years after chronic GVHD diagnosis). Exclusion criteria include primary disease relapse and inability to comply with study procedures.

Clinicians and patients report standardized information on chronic GVHD organ involvement and symptoms at cohort enrollment and at serial follow-up visits. Chronic GVHD global severity according to the NIH Chronic GVHD Consensus is scored according to objective criteria for each organ involved, which is summarized for an overall score of mild, moderate, or

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Table 1
Summary of Patient and Transplantation Characteristics

Characteristics	Category	Count (%)	Median	Min	Max
Site	Fred Hutchinson Cancer Research Center	247 (44%)			
	University of Minnesota	59 (10%)			
	Dana-Farber Cancer institute	65 (11%)			
	Stanford University Medical Center	72 (13%)			
	Northwest Children's Hospital	13 (2%)			
	Vanderbilt University Medical Center	47 (8%)			
	Medical College of Wisconsin	23 (4%)			
	Washington University Medical Center	4 (1%)			
	Moffitt Cancer Center	35 (6%)			
	Memorial Sloan-Kettering Cancer Center	2 (1%)			
Case type	Incident	336 (59%)			
	Prevalent	231 (41%)			
Adult or children	Adult (18+)	553 (98%)			
	Pediatric (2-17)	14 (2%)			
Patient age at registration (yr)			51.0	2.0	79.0
Patient age at transplant (yr)			50.2	1.3	78.9
Patient gender	Female	241 (43%)			
	Male	326 (57%)			
Patient race	Black	16 (3%)			
	American Indian/Alaskan Native	2 (<1%)			
	Asian	25 (4%)			
	Native Hawaiian/Pacific Islander	2 (<1%)			
	White	510 (90%)			
	Multirace	7 (1%)			
	Unknown	5 (1%)			
Ethnicity (n = 565)	Hispanic	29 (5%)			
	Not Hispanic	536 (95%)			
Months from transplant to enrollment			11.9	2.9	294.2
Months from transplant to chronic GVHD onset			7.3	1.2	291
Months from chronic GVHD onset to enrollment			1.8	0	32.5
Diagnosis	AML	190 (34%)			
	ALL	66 (12%)			
	CML	29 (5%)			
	CLL	46 (8%)			
	MDS	84 (15%)			
	NHL	80 (14%)			
	HD	17 (3%)			
	MM	29 (5%)			
	AA	7 (1%)			
	Other	19 (3%)			
Disease status at transplant (n = 563)	Early	184 (33%)			
	Intermediate	241 (43%)			
	Advanced	138 (24%)			
Graft source	Bone marrow	38 (7%)			
	Cord blood	26 (4%)			
	Peripheral blood	503 (89%)			
Conditioning type (n = 564)	Myeloablative	326 (58%)			
	Nonmyeloablative	238 (42%)			
Donor-patient CMV status (n = 562)	Patient and donor CMV both negative	188 (33%)			
	Patient or donor CMV positive	374 (67%)			
Donor-patient gender combination (n = 562)	Female into male	164 (29%)			
	Others	398 (71%)			
Donor match (n = 565)	Matched related	240 (42%)			
	Matched unrelated	236 (42%)			
	Mismatched	89 (16%)			
Prior acute GVHD	Yes	376 (66%)			
	No	191 (34%)			
Karnofsky performance score at onset	80% +	348 (61%)			
	< 80%	95 (17%)			
	Missing	124 (22%)			

GHVD indicates graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; HD, Hodgkin lymphoma; MM, multiple myeloma; AA, aplastic anemia; CMV, cytomegalovirus.
N = 567 unless otherwise specified.

severe [16]. Additional measures examine the impact of chronic GVHD on patients' functional ability, symptom burden, and QOL. The assessments performed reflect the recommendations of the NIH Consensus Conference and are described briefly in the following sections and in the published cohort study rationale and design summary [17].

Functional Assessments

Functional measures examined in this analysis include standardized hand grip strength and 2-minute walk test. In the assessment of grip strength, a series of 3 measurements are made using a portable electronic dynamometer [18,19]. In the conduct of the 2-minute walk test, the patient is instructed to walk a 50-foot course with 180° turns at each end, and the total distance covered is recorded [19-21].

Patient-Reported Outcomes

The Lee Chronic GVHD Symptom Scale is a 30-item, 7-subscale symptom scale that evaluates adverse effects of chronic GVHD on skin, vitality, lung, nutritional status, psychological functioning, eye, and mouth symptoms [22]. The Human Activity Profile (HAP) is a 94-item self-reported assessment of energy expenditure and physical fitness. The instrument was first