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Colonoscopy and Sigmoidoscopy are Equally Effective for the Diagnosis of Colonic Acute Graft-versus-Host Disease in Patients with Diarrhea after Allogeneic Stem Cell Transplantation: A Prospective Controlled Trial

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Colonic acute graft-versus-host disease (aGVHD) affects approximately 10% of patients who have undergone allogeneic stem cell transplantation (allo-SCT). Diarrhea is a major clinical sign but also a common post-transplantation symptom in these patients. Comprehensive histopathologic examination of the colon is therefore regarded as crucial to establish a diagnosis, but the colonic segment that should be targeted for a diagnostic biopsy remains a topic of debate. The primary objective of this study was to compare prospectively colonoscopy with sigmoidoscopy regarding their capabilities to provide a histopathologically proven diagnosis of colonic aGVHD. Thirty-seven allo-SCT patients with diarrhea all underwent a colonoscopy. All biopsies collected from the descending colon were regarded as also attainable by sigmoidoscopy, whereas biopsies collected in regions further up the colon (from the transverse and ascending colon) were regarded as acquirable exclusively by colonoscopy. Biopsies attainable by colonoscopy and sigmoidoscopy were positive for GVHD in 25 (68%) and 24 (65%) patients, respectively (95% confidence interval for difference of proportions, −.185 to .245; $P = .978$; $z = .0271$ by the z-test). Sigmoidoscopy is as effective as colonoscopy in establishing a diagnosis of colonic aGVHD in patients who have diarrhea after allo-SCT.

INTRODUCTION

Gastrointestinal (GI) acute graft-versus-host disease (aGVHD) affects approximately 20% to 50% of patients who undergo allogeneic stem cell transplantation (allo-SCT) when the diagnosis is based primarily on clinical symptoms and findings [1,2]. The prognosis for certain high-risk patients can be very poor [3]. In patients with aGVHD of the lower GI tract, diarrhea is the main symptom, frequently accompanied by abdominal pain and/or bleeding. Measurement of the volume of diarrhea is essential for evaluating the grade of disease, which is inversely correlated with survival [4,5].

Because diarrhea is a common post-transplantation symptom, it is essential to distinguish patients with colonic aGVHD from patients who have other treatable conditions, such as cytomegalovirus (CMV) colitis, the course of which may be exacerbated by treatments that entail increased immunosuppression. Therefore, histopathology has become a critical tool in establishing a diagnosis of intestinal aGVHD. Although not diagnostic of GVHD, the cardinal histopathologic criterion is the presence of epithelial single-cell necrosis (apoptosis) that may or may not be accompanied by increased inflammation and reactive accompanying epithelial changes or loss [6-9]. In a previous report, the incidence of colonic aGVHD was found to be approximately 10%, based on histopathologic findings [10]. However, the colonic segment that should be targeted for a diagnostic biopsy remains a topic of debate [11-13], and prospective trials to address this issue are lacking.

The only way to obtain biopsies from the entire colon is to perform a colonoscopy. However, preparation for this procedure is challenging for both patients and clinical staff. The alternative to colonoscopy is sigmoidoscopy, for which the

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preparation is less extensive and the procedure itself is less onerous and time-consuming than colonoscopy. However, because only a portion of the target organ is examined, there is a potential risk of missing the characteristic histopathologic findings and thereby underdiagnosing colonic GVHD in case this is not regarded to be a pan-colonic disease. In the controlled clinical trial described here, we prospectively compared biopsies attainable by colonoscopy with biopsies attainable by sigmoidoscopy to see whether we could obtain a histopathologically proven colonic GVHD diagnosis in adult patients with diarrhea after allo-SCT.

METHODS

Patients

Between May 2004 and January 2013, 248 adult patients (≥18 years of age) underwent allo-SCT at the department of Hematology and Coagulation at Sahlgrenska University Hospital, Göteborg, Sweden. Thirty-seven patients were included in the study. The inclusion criterion was significant diarrhea with or without abdominal pain and/or bleeding, nausea, or vomiting any time after allo-SCT.

During the study interval 18 additional patients underwent sigmoidoscopy, of whom 8 fulfilled the inclusion criterion but were not included because of missed informed consent (n = 3) or at the discretion of the responsible clinician (patients could not manage the preparation procedure for a colonoscopy; n = 5). Five of these 8 patients (63%) exhibited positive histopathology for GVHD. The remaining 10 patients who underwent sigmoidoscopy did not fulfill the inclusion criterion but instead had more unspecific GI symptoms like abdominal pain and/or rectal bleeding. A GVHD diagnosis could not be established in any of these 10 cases.

Patients without diarrhea who instead *only* had symptoms from the upper GI tract (anorexia, nausea, vomiting, upper abdominal pain, and early satiety) routinely underwent a gastroduodenoscopy and were not included in the study. Seven of the 37 included patients underwent a gastroduodenoscopy during the study but only in 1 case in connection with the colonoscopy. In this single case histopathologic evidence of gastric/duodenal GVHD could be established but not in the remaining 6 cases.

Patient characteristics are presented in Table 1. All patients gave informed consent before inclusion.

Clinical Grading

Findings consistent with aGVHD of the skin and liver were recorded prospectively, and overall aGVHD was staged and graded according to established criteria [4,5]. Intestinal stage and grade were based on the maximal daily volume of diarrhea (rounded to the nearest 100 mL) and the presence of any bleeding. Stool samples were examined for bacteria (including culturing for *Clostridium difficile*), fungi, and viruses (PCR for calicivirus, adenovirus, astrovirus, and rotavirus), although colonoscopy was not delayed to wait for these results.

Endoscopic Preparation and Grading

All 37 patients underwent a colonoscopy (Olympus CF160L or Olympus CF 180L; Olympus, Tokyo, Japan), with procedures performed by 7 different experienced endoscopists. The preparation for the procedure included oral administration of 2 to 4 L polyethylene glycol (Laxabon; BioPhausia, Stockholm, Sweden), except for 2 patients who instead received orally (2 × 45 mL) disodium phosphate dodecahydrate/sodium dihydrogen phosphate dehydrate (Phosphoral; CCS Healthcare, Borlange, Sweden). One patient was excluded from the study because the examination was terminated before the entire colon could be examined. It was at the discretion of the responsible clinician to decide if treatment with cortisone could be postponed until after the colonoscopy.

As a minimum, 2 biopsies were collected according to a specific study algorithm from each of the following sites: ascending colon, transverse colon, and descending colon (for a minimum of 6 biopsies per patient). The biopsies were taken preferentially from areas that showed macroscopic changes or otherwise from areas with normal endoscopic findings. Based on the endoscopic findings, macroscopic grading was performed using a 4-point scale adapted from Cruz-Correa et al. [9] (Table 2).

All biopsies collected from the descending colon (up to the left colic flexure) were regarded as attainable by sigmoidoscopy, whereas biopsies collected in regions further up the colon (from the transverse and ascending colon) were regarded as attainable exclusively by colonoscopy. Thus, all 37 patients were regarded to have undergone both sigmoidoscopy and colonoscopy on the same occasion, and, accordingly, each patient served as their own control (for a total of 37 matched pairs).

Table 1
Patient Characteristics

	Positive Histopathology (n = 25)	Negative Histopathology (n = 12)	*P*
Median age, yr (range)	53 (32-65)	60 (20-68)	.42
Gender			
Male	14 (56)	7 (58)	.81
Female	11 (44)	5 (42)	
Diagnosis			
Acute leukemia/MDS	11 (44)	5 (42)	—
CML	3 (12)	3 (25)	
CLL/lymphoma	9 (36)	2 (17)	
MPD	1 (4)	2 (17)	
Hemophagocytosis	1 (4)	0	
Conditioning			
MAC	8 (32)	5 (42)	.82
RIC	17 (68)	7 (58)	
Donor			
Related	10 (40)	3 (25)	.60
Matched unrelated	15 (60)	9 (75)	
Stem cell source			
Peripheral blood	24 (96)	11 (92)	.78
Bone marrow	1 (4)	1 (8)	
Median CD34 content, $\times 10^6$/kg (range)	4.0 (3.0-6.5)	4.4 (1.3-6.9)	.91
Median serum albumin concentration, g/L (range)	36 (14-48)	42 (31-46)	.25
Number of biopsies per patient (range)	11 (6-24)	10 (6-23)	.77
Interval between transplant and colonoscopy, days (range)	96 (19-715)	63 (19-852)	.45

MDS indicates myelodysplastic syndrome; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; MPD, myeloproliferative disorder; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; —, not siignificant
Values are total number of cases with percents in parentheses, unless otherwise noted.

Histopathologic Preparation and Grading

All mucosal biopsy specimens were fixed in 4.5% buffered formalin and stained with hematoxylin and eosin as well as being routinely stained for CMV. The same experienced pathologist conducted a nonblinded evaluation of sections from all 421 biopsy samples. Based on this evaluation, histologic grading was performed using a 4-point validated scale adapted from Cruz-Correa et al. [9] (Table 3). Assignment of a histologic grade of 1 or higher (>2 apoptotic cell bodies per cryptic profile) was considered to be suggestive of aGVHD. The detection of ≤2 apoptotic bodies per cryptic profile was regarded as a nonspecific finding and as not being consistent with a diagnosis of aGVHD in this study.

Statistical Analyses

The primary statistical outcome in the study was colonic aGVHD based on a positive biopsy (grades 1 to 4). The required number of patients was based on a study of dependent variables with paired observations and a 2-sided alternative hypothesis with a significance level of 5%. The incidence of colonic GVHD was estimated to be 10% in the population studied. To obtain 80% power, it was calculated that 37 paired observations (74 observations in total) were required. Continuous and categorical variables were analyzed using the Mann-Whitney U-test and Fisher's exact test, respectively. When comparing percentages across groups, a z-test was used.

Table 2
Endoscopic Grading of GI GVHD

Grade	Finding
0	Normal
1	Loss of vascular markings and/or presence of focal mild erythema
2	Moderate edema and/or erythema
3	Edema, erythema, erosions, and/or bleeding
4	Ulceration, exudates, and bleeding

The endoscopic image was graded as positive (grades 1-4) or negative (grade 0) for GI GVHD according to a validated scale adapted from Cruz-Correa et al. [9].