6. Lerut J, Bourlier P, de Ville de Goyet J, et al. Improvement of technique for adult orthotopic liver retransplantation. J Am Coll Surg 1995; 180: 729.
7. Calne RY, Williams R. Liver transplantation in man: observations on technique and organization in five cases. BMJ 1968; 4: 535.
8. Bismuth H, Castaing D, Sherlock DJ. Liver transplantation by face-à-face vena cavaplasty. Surgery 1992; 111: 151.
9. Cherqui D, Lauzet JY, Rotman N, et al. Orthotopic liver transplantation with preservation of the caval and portal flows. Transplantation 1994; 58: 793.
10. Fleitas MG, Casanova D, Martino E, et al. Could the piggy-back operation in liver transplantation be routinely used? Arch Surg 1994; 129: 842.
11. Iovine E, Mazziotti A, Grazi GL, et al. Piggy-back versus conventional technique in liver transplantation: report of a randomized trial. Transpl Int 1997; 10: 109.
12. Busque S, Esquivel CO, Concepcion W, et al. Experience with the piggy-back technique without caval occlusion in adult orthotopic liver transplantation. Transplantation 1998; 65: 77.
13. Gerunda GE, Merenda R, Neri D, et al. Liver transplantation with vena cava in situ and selective use of temporary portacaval shunt or portal clamping. Hepatogastroenterology 2001; 48: 486.
14. Navarro F, Le Moine MC, Fabre JM, et al. Specific vascular complications of orthotopic liver transplantation with preservation of the retrohepatic vena cava: review of 1361 cases. Transplantation 1999; 68: 646.
15. Parrilla P, Sanchez-Bueno F, Figueras J, et al. Analysis of the complications of the piggy-back technique in 1112 liver transplants. Transplantation 1999; 67: 1214.
16. Reddy KS, Johnston TD, Putnam LA, et al. Piggy-back technique and selective use of veno-venous bypass in adult orthotopic liver transplantation. Clin Transplant 2000; 14: 370.
17. Steib A, Saada A, Clever B, et al. Orthotopic liver transplantation with preservation of portocaval flow compared with venovenous bypass. Liver Transplant Surg 1997; 5: 518.
18. Shokouh-Amiri MH, Gaber AO, Bagous WA, et al. Choice of surgical technique influences perioperative outcomes in liver transplantation. Ann Surg 2000; 231: 814.
19. Hesse UJ, Berrevoet F, Troisi R, et al. Hepato-venous reconstruction in orthotopic liver transplantation with preservation of the recipient's inferior vena cava and veno-venous bypass. Langenbecks Arch Surg 2000; 385: 350.
20. Cirera I, Navasa M, Rimola A, et al. Ascites after liver transplantation. Liver Transpl 2000; 6: 157.
21. Ducerf C, Rode A, Adham M, et al. Hepatic outflow study after piggyback liver transplantation. Surgery 1996; 120: 484.
22. Lerut J, Gertsch Ph. Side-to-side cavo-cavostomy: a useful aid in "complicated" piggy-back liver transplantation. Transpl Int 1993; 6: 299.
23. Merhav H, Bronsther O, Pinna A, et al. Significant stenosis of the vena cava following liver transplantation: a six years experience. Transplantation 1993; 56: 1541.
24. Figueras J, Llado L, Ramos E, et al. Temporary portocaval shunt during liver transplantation with vena cava preservation. Results of a prospective randomized study. Liver Transpl 2001; 7: 904.
25. Figueras J, Sabate A, Fabregat J, et al. Haemodynamics during the anhepatic phase in orthotopic liver transplantation with vena cava preservation: a comparative study. Transplant Proc 1993; 25: 2588.
26. Durand F, Aschebourg J, Sauvanet A, et al. Preservation of renal perfusion and postoperative renal function by side-to-side cavo-caval anastomosis in liver transplant recipients. Transpl Int 1995; 5: 407.
27. Rossaint R, Slama K, Jaeger M, et al. Fluid restriction and early extubation for successful liver transplantation. Transplant Proc 1990; 22: 1533.
28. Mc Alister VC, Grant DR, Roy A, et al. Right phrenic nerve injury in orthotopic liver transplantation. Transplantation 1993; 55: 826.
29. Lerut J, de Ville de Goyet J, Donataccio M, et al. Piggy-back transplantation with side-to-side cavocavostomy is an ideal technique for right split liver allograft implantation. J Am Coll Surg 1994; 179: 573.

IMPROVEMENT OF INFLAMMATORY BOWEL DISEASE AFTER ALLOGENEIC STEM-CELL TRANSPLANTATION

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Because causes of inflammatory bowel disease (IBD) remain obscure and a curative therapy is still lacking, the influence of stem-cell transplantation (SCT) on IBD is of major interest. We retrospectively analyzed the course of seven patients with Crohn's disease and four patients with idiopathic ulcerative colitis who underwent allogeneic SCT between July 1994 and August 2002 for acute and chronic myeloid leukemia and myelodysplastic syndrome. After a median follow-up of 34 months posttransplantation, 10 patients are alive. None of the patients showed IBD activity after SCT, except one patient with mild persistent symptoms of Crohn's disease early after transplant. Colonoscopy after complete discontinuation of prophylactic posttransplant immunosuppression revealed no pathologic findings. These observations imply that host immune dysregulation plays a central role in the perpetuation of IBD. It may be influenced by the implementation of a new allogeneic immune system resulting from the transplantation of hematopoietic stem cells.

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Crohn's disease and ulcerative colitis are idiopathic inflammatory bowel diseases (IBDs) characterized by a dysregulated mucosal immune response to luminal antigens that leads to chronic inflammation of the intestine (*1*). Current therapies attempt to modulate the immune processes to induce remissions of active disease, maintain remission, and prevent relapse (*2*). The pathogenic mechanisms of IBD are still poorly understood. However, there is evidence that in addition to genetic susceptibility and environmental stimuli, abnormal T-cell responses and overwhelming secretion of proinflammatory mediators disturb the homeostatic defenses of the gut, resulting in epithelial injuries. Experimental animal data and clinical case reports of remissions of IBD (*3*) and autoimmune diseases (*4*, *5*) observed after stem-cell transplantation (SCT) for severe hematologic diseases indicate allogeneic hematopoietic SCT as a possible therapeutic

option (*6*). In this retrospective descriptive study, we analyzed our experiences with allogeneic bone marrow and peripheral blood SCT in 11 patients with hematologic diseases and coexistent IBD. We evaluated the clinical course of IBD after transplantation and assessed whether this treatment modality demonstrates any effects on intestinal inflammatory activity.

PATIENTS AND METHODS

The patients' characteristics are shown in Tables 1 and 2. All the patients underwent allogeneic SCT as the result of chronic myeloid leukemia (CML) in the first chronic phase, except one patient with acute myeloid leukemia and one patient with drug-induced secondary myelodysplastic syndrome resulting from azathioprine treatment of her preexistent Crohn's disease. Patients received myeloablative therapy with either total body irradiation (10–12 Gy) in combination with high-dose cyclophosphamide (seven patients), thiotepa (two patients), and antithymocyte globulin (one patient) or chemotherapy alone with busulfan and cyclophosphamide (two patients). Four patients underwent transplantation with stem cells collected from the peripheral blood, four patients received unmodified bone marrow, and three patients received CD-34 enriched, T-cell–depleted peripheral blood stem cells. All the patients were human leukocyte antigen-identical (six of them related sibling donors), except for one mismatched unrelated donor. For the prevention of acute graft-versus-host disease (GVHD), patients who received transplants with bone marrow and non-T-cell–depleted peripheral blood stem cells were treated with cyclosporine A and methotrexate. Acute GVHD was treated with methylprednisolone (1–3 mg/kg) until disease activity abated. In addition to the clinical presentation, the pretransplant diagnosis of IBD was confirmed by endoscopic and histologic findings in all the patients. The activity of intestinal inflammation before the start of transplant conditioning was determined clinically by the presence of diarrhea, abdominal pain, and recent endoscopic and histologic records if available. Patients were classified as having low or highly active or inactive disease. After transplantation, endoscopic controls were conducted in patients with persistent diarrhea and abdominal pain to enforce a causal diagnosis based on histologic criteria. Two patients underwent routine colonoscopy after the discontinuation of prophylactic immunosuppression.

TABLE 1. Characteristics of patients with inflammatory bowel disease and allogeneic transplantation

Number of patients	11
Male/female	5/6
Age (yr) at diagnosis of IBD (median; range)	25 (16–44)
Crohn's disease	7
Ulcerative colitis	4
Time (yr) of IBD history pretransplant (median; range)	10 (0.5–22)
Immunosuppressive medication at transplantation	4
No disease activity at transplantation	5
Low disease activity at transplantation	6
Surgical therapy pretransplant	4
Complications of IBD	
Enterocutaneous fistula	3
Enterostenosis	2
Arthropathy	1
Psoriasis vulgaris	1
No disease activity after transplantation	10
Persistence of IBD after transplantation	1
Endoscopic control after transplantation	6
Follow-up after transplant (mo) (median; range)	34 (3–117)
Recurrence of IBD after transplantation	0
Patients alive	10

IBD, inflammatory bowel disease.

TABLE 2. Summary of transplantation-related data

	Number of patients
Hematologic malignancy	
CML	9
AML	1
Secondary MDS	1
Age (yr) at transplantation (median; range)	41 (27–55)
Donor match	
HLA-identical sibling donor	8
HLA-identical unrelated donor	2
Mismatched unrelated donor	1
Transplantation type	
Bone marrow transplantation	4
Unmanipulated peripheral blood SCT	4
CD34-purified SCT	3
Conditioning regimen	
TBI+cyclophosphamide	6
TBI+cyclophosphamide+ATG	1
TBI+cyclophosphamide+ATG+thiotepa	1
TBI+cyclophosphamide+thiotepa	1
Busulfan+cyclophosphamide	2
GVHD prophylaxis	
T-cell depletion	3
Cyclosporine A+methotraxate days 1, 3, 6, and 11	8
Acute GVHD (grades I and II)	8
Acute GVHD (grades III and IV)	0
Chronic GVHD	0
Discontinuation of immunosuppression after transplant	2
Cytogenetic relapse	3
Complete chimerism	11
Minimal residual disease	0

GVHD, graft-versus-host disease; ATG, antithymocyte globulin; SCT, stem-cell transplantation; HLA, human leukocyte antigen; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; TBI, total body irradiation.

RESULTS

At the time of conditioning, six patients were found to demonstrate low activity of intestinal inflammation with up to five stools daily and mild abdominal pain. Four of them were receiving anti-inflammatory medication with sulfasalazine or low doses of steroids or both. During the conditioning and the neutropenic phase after transplantation, no exacerbation of IBD was observed in any of the patients. No other abdominal complications, such as increased intestinal toxicity, were documented during the pretransplant course, even in patients with a history of multiple surgical interventions because of visceral complications. Only one patient showed signs of hemorrhagic colitis after conditioning with total body irradiation, cyclophosphamide, and thiotepa, which was self-limiting during the further clinical course. After a median follow-up period of 34 months posttransplantation, 10 pa-

tients are alive; all patients are in complete remission of their hematologic malignancy and free of IBD symptoms. One male patient with CML who received a transplant with stem cells from an unrelated donor died 10 months after peripheral blood SCT because of pulmonary fungal infection. Endoscopy in this patient, because of suggested acute intestinal GVHD 3 months posttransplant, revealed ileocecal erosive lesions that macroscopically resembled infectious colitis. Histology and virology confirmed cytomegalovirus enteritis, and the patient became asymptomatic after antiviral therapy. The patient remained free of IBD until he died. In three patients who received CD34-enriched transplants, donor lymphocyte infusions as the result of a transient cytogenetic CML relapse did not result in a recurrence of intestinal inflammation. One patient showed clinical signs of ulcerative colitis 11 months after transplantation. Endoscopy and intestinal biopsy did not confirm ulcerative colitis but revealed unspecific minor chronic inflammation. Symptoms of intestinal irritation diminished completely under supportive therapy, and the patient remains free of IBD 48 months posttransplant. In one female patient with a low activity of Crohn's disease who received 5 mg steroids pretransplant, IBD symptoms persisted 1 month after transplant under second-line GVHD prophylaxis with FK509 and steroids (2 mg/kg body weight). Colonoscopic and gastroscopic evaluation macroscopically showed inflammatory lesions not typical for Crohn's disease nor for GVHD but revealed *Helicobacter pylori*-associated chronic gastritis and loss of covering epithelium with stromal fibrosis in the small gut and colon. After the complete discontinuation of prophylactic immunosuppression in two patients, we evaluated the absence of bowel inflammation by endoscopy. No pathologic findings were observed. In two of the patients who suffered from IBD-related arthropathy and psoriasis vulgaris, these symptoms resolved completely after transplantation.

DISCUSSION

Our data on the posttransplant course of 11 patients with IBD demonstrate the absence of chronic intestinal inflammation in 10 of 11 patients. Within a follow-up period of 3 to 117 months, there were no signs of IBD relapse after allogeneic SCT. Only one female patient with Crohn's disease showed persistence of mild intestinal inflammation early after transplant despite immunosuppressive treatment. However, the follow-up in this case was rather short, and IBD was not confirmed histologically. In addition, after a 10-year history of Crohn's disease in this patient, structural changes of the gut mucosa may render its recovery more difficult. Our observations show that improvement of IBD was independent of donor match, conditioning regimen, stem-cell source, occurrence of acute GVHD, or cytogenetic leukemic relapse. Furthermore, our findings verify that patients with IBD do not seem to be at increased risk for intestinal complications because of the toxic side effects of conditioning therapy.

These observations are consistent with previous case reports of patients with Crohn's disease or ulcerative colitis who underwent allogeneic marrow transplantation (*3*). Despite a median follow-up period of just 34 months, allogeneic SCT seems to improve IBD, which might be an effect of multiple factors: Conditioning therapy is myeloablative and immunoablative, there is often long-term immunosuppression after transplantation to prevent acute or chronic GVHD, and the original bowel flora is temporarily altered after total gut decontamination and long-term antibacterial and antifungal treatment. However, the most important aspect seems to be the modification of a genetically determined immune abnormality that is responsible for the chronic intestinal inflammation by the implementation of a new allogeneic immune system. This is demonstrated by the fact that even after withdrawal of prophylactic immunosuppression, no signs of recurrent IBD were observed. Patients who underwent transplantation with CD34-purified peripheral blood stem cells were free of any immunosuppressive drugs from the beginning because the transplants were T-cell depleted. Reconstitution of the immune system then was ensured by donor T-lymphocyte add-backs.

Allogeneic bone marrow transplantation has also resulted in the remission of several other autoimmune diseases (*4*, *5*). Conversely, it seems to be possible that ulcerative colitis or autoimmune phenomenons can be transferred from donor to recipient (*7*). Allogeneic SCT may provide an approach for overcoming IBD: The host immune system is destroyed by myeloablative or immunoablative conditioning, and a new sufficient immune system is replaced. Further prospective studies are necessary to determine if allogeneic SCT using innovative conditioning regimens or stem-cell purified, T-cell–depleted transplants might become a curative option for severe, refractory IBD.

REFERENCES

1. Hanauer SB, Dassopoulos T. Evolving strategies for inflammatory bowel disease. Annu Rev Med 2001; 52: 299–318.
2. Rutgeerts P. Medical therapy of inflammatory bowel disease. Digestion 1998; 59: 453–469.
3. Lopez-Cubero SO, Sullivan KM, McDonald GB. Course of Crohn's disease after allogeneic marrow transplantation. Gastroenterology 1998; 114: 433–440.
4. Marmont AM. New horizons in the treatment of autoimmune diseases. Annu Rev Med 2000; 51: 115–134.
5. Ikehara S. Bone marrow transplantation for autoimmune diseases. Acta Heamatol 1998; 99: 116–132.
6. Hawkey CJ, Snowden JA, Lobo A, et al. Stem cell transplantation for inflammatory bowel disease: practical and ethical issues. Gut 2000; 46: 869–872.
7. Baron FA, Hermanne JP, Dowlati A, et al. Bronchiolitis obliterans organizing pneumonia and ulcerative colitis after allogeneic bone marrow transplantation. Bone Marrow Transplant 1998; 21(9): 951–954.