REPORT

Transplantation for Autoimmune Diseases in North and South America: A Report of the Center for International Blood and Marrow Transplant Research

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Hematopoietic cell transplantation (HCT) is an emerging therapy for patients with severe autoimmune diseases (AID). We report data on 368 patients with AID who underwent HCT in 64 North and South American transplantation centers reported to the Center for International Blood and Marrow Transplant Research between 1996 and 2009. Most of the HCTs involved autologous grafts (n = 339); allogeneic HCT (n = 29) was done mostly in children. The most common indications for HCT were multiple sclerosis, systemic sclerosis, and systemic lupus erythematosus. The median age at transplantation was 38 years for autologous HCT and 25 years for allogeneic HCT. The corresponding times from diagnosis to HCT were 35 months and 24 months. Three-year overall survival after autologous HCT was 86% (95% confidence interval [CI], 81%-91%). Median follow-up of survivors was 31 months (range, 1-144 months). The most common causes of death were AID progression, infections, and organ failure. On multivariate analysis, the risk of death was higher in patients at centers that performed fewer than 5 autologous HCTs (relative risk, 3.5; 95% CI, 1.1-11.1; $P = .03$) and those that performed 5 to 15 autologous HCTs for AID during the study period (relative risk, 4.2; 95% CI, 1.5-11.7; $P = .006$) compared with patients at centers that performed more than 15 autologous HCTs for AID during the study period. AID is an emerging indication for HCT in the region. Collaboration of hematologists and other disease specialists with an outcomes database is important to promote optimal patient selection, analysis of the impact of prognostic variables and long-term outcomes, and development of clinical trials.

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INTRODUCTION

The rationale for hematopoietic stem cell transplantation (HCT) to treat autoimmune diseases (AID) is to deplete autoreactive immune effector cells through a combination of high-dose immunosuppressive therapy and rescue by infusion of autologous or

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Table 1. Characteristics of Recipients of Autologous HCT for Treatment of AID between 1996 and 2009

Characteristic	Value
Transplantation centers represented, n	53
Patients, n	339
Age, years, median (range)	39 (6-64)
Age group, years, n (%)	
≤10	4 (1)
11-20	28 (8)
21-30	49 (14)
31-40	91 (27)
41-50	120 (33)
≥51	47 (13)
Female sex, n (%)	196 (58)
Diagnosis, n (%)	
MS	160 (47)
SSC	97 (29)
SLE	27 (8)
Rheumatoid arthritis	10 (3)
Autoimmune cytopenia	7 (2)
Myasthenia gravis	3 (1)
Diabetes mellitus	22 (7)
Other*	13 (4)
Time from diagnosis to HCT, months, median (range)	52 (<1-413)
Conditioning regimen, n (%)	
Cyclophosphamide + ATG ± others	140 (41)
Cyclophosphamide y + total body irradiation + ATG	107 (31)
BEAM + ATG ± others	42 (12)
Cyclophosphamide y + total body irradiation	13 (4)
Total lymphoid irradiation + ATG ± others	13 (4)
Busulfan + cyclophosphamide ± others	10 (3)
Fludarabine + cyclophosphamide ± others	10 (3)
Melphalan	4 (1)
Graft source, n (%)	
Bone marrow	3 (1)
Peripheral blood	336 (99)
Graft manipulation, n (%)	
No	188 (56)
Yes†	143 (42)
Unknown	8 (2)
Year of HCT, n (%)	
1996-2000	81 (24)
2000-2004	140 (41)
2005-2009	118 (35)
Follow-up of survivors, months, median (range)	31 (<1-144)

ATG indicates antithymocyte globulin; BEAM, carmustine, etoposide, cytarabine, and melphalan.
*Diagnosis, other: connective tissue disease not specified (n = 3), other autoimmune disease unclassified (n = 8), Crohn disease (n = 1), and Sjögren syndrome (n = 1).
†$CD34^+$ cell selection.

allogeneic hematopoietic cells that give rise to a new immunocompetent immune system with less or no autoreactivity [1,2]. Clinical interest in this approach began in the mid-1990s, based on data from experimental models and pilot studies of autologous HCT in patients with severe or refractory multiple sclerosis (MS), systemic sclerosis (SSC), rheumatoid arthritis, and systemic lupus erythematosus (SLE) [3-8]. International guidelines were first issued in 1997 [9]. Sustained remissions are achieved in approximately one-half of patients despite full immunologic reconstitution, avoiding the need for additional disease-modifying treatments [10]. Increasing experience and better patient selection has led to a reduction in HCT-related morbidity and mortality, mainly in patients with MS [11]. Progress in conventional and experimental therapies has not dampened the enthusiasm for HCT, which offers the prospect of a one-time intervention for deadly or disabling chronic disease [10,12,13]. Experience with allogeneic HCT for AID is limited [14-19]. Allografting has the potential to replace the recipient immune system but at a higher mortality rate, a major concern in treating patients with nonmalignant diseases [16,17,20-22].

Use of HCTs in AID is typically considered only in patients with severe diseases who have failed other therapies. Approximately 1,300 HCTs, mostly autologous, for AID have been performed in Europe since 1995 [10]. Conversely, in the Americas, published activity is limited by single-center experience or clinical trials. This article reports HCTs in patients with AID in North and South American transplantation centers registered with the Center for International Blood and Marrow Transplant Research (CIBMTR). Our objective is to evaluate the HCTs performed for this indication in the Americas and provide an impetus for further research and clinical activity [23].

METHODS

Data Sources

This report summarizes data reported to the CIBMTR, the Seattle Consortium, and 2 Brazilian centers. The CIBMTR was established in 2004 through a formal affiliation of the research division of the National Marrow Donor Program and the International Bone Marrow Transplant Registry of the Medical College of Wisconsin. Demographic data, disease and transplantation characteristics, and outcome data are collected on all consecutive HCTs at more than 400 participating centers. Computerized error checks, physician review of submitted data, and onsite audits of participating centers ensure data quality. Because 3 centers with active HCT programs for AID were not active CIBMTR centers for the entire study period, additional data were provided by them specifically for this report. These 3 centers are Fred Hutchinson Cancer Research Center in Seattle and 2 Brazilian centers, Faculdade de Medicina de Ribeirão Preto and Albert Einstein Hospital in São Paulo. Observational studies conducted by the CIBMTR are performed in compliance with HIPAA privacy rules as a public health authority and also in compliance with all applicable federal regulations pertaining to the protection of human research participants as determined by continuous review of the Medical College of Wisconsin's Institutional Review Board since 1985. Additional data not previously reported to the CIBMTR were submitted by these 3 centers for patients who provided written consent to participate in local clinical trials [24,25].

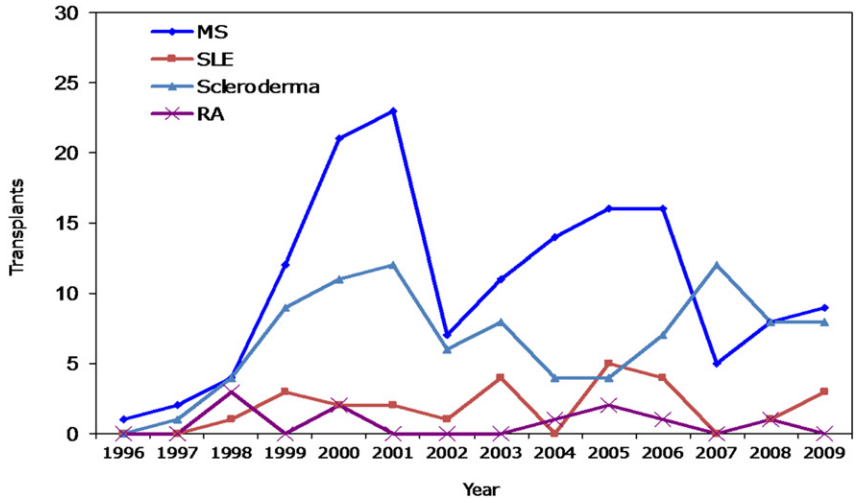

Figure 1. Annual HCTs for AID by indication between 1996 and 2009.

Patients

HCT for AID was first reported to the CIBMTR in 1996. All consecutive HCTs (n = 204) for AID performed between 1996 and 2009 by centers with an active CIBMTR data use agreement were included in this study (Table 1). Cases reported to the CIBMTR from centers without an active data use agreement (n = 114) were excluded. Patients enrolled in three prospective clinical trials at the Fred Hutchinson Cancer Research Center were also included in this study (n = 62). Details from these trials have been reported elsewhere [8,26-28]. The 2 Brazilian transplantation centers provided data on 97 consecutive patients who underwent HCT for AID under the same disease-specific protocols from 1998 through 2007 [24]. Twenty-four patients (11 from the Seattle Consortium and 13 from the Brazilian centers) were also reported to the CIBMTR. Duplicate records were removed before the analyses; thus, the total study population comprised 339 patients.

Table 2. Causes of Death after Autologous HCT for AID

Disease	Cause of Death	Number
Evans syndrome (n = 1)	AID	1
Idiopathic thrombocytopenic purpura (n = 2)	AID	1
	Bleeding	1
MS (n = 11)	AID	4
	Bleeding	2
	Infection	1
	Myelodysplasia*	1
	Organ failure	1
	Thrombotic thrombocytopenic purpura	1
	Unknown	1
SSC (n = 16)	AID	4
	Organ failure	4
	Bleeding	2
	Cancer	2
	Infection	2
	Unknown	2
SLE (n = 8)	Infection	6
	AID	1
	Graft failure	1

*Patient developed myelodysplasia after autologous HCT, proceeded to allogeneic HCT, and died from persistent myelodysplasia.

Statistical Analysis

Demographic data were summarized with descriptive statistics. Categorical variables are reported as absolute numbers and percentage of total patients, and continuous variables are reported as median and range. To ensure sufficient long-term follow-up, survival analyses were restricted to patients who underwent HCT between 1996 and 2007. Overall survival curves were calculated using a Kaplan-Meier estimator, and the variance was determined using Greenwood's formula [29]. In addition, a Cox proportional hazards model for overall mortality after autologous HCT was built with covariates selected using a stepwise approach for $P < .05$. The proportionality assumption of Cox models was checked. Covariates considered for the model include age, sex, disease (MS, SSC, SLE, and other), year of transplantation, number of HCTs for AID performed at the transplant center during the study period, and time from diagnosis of AID to HCT. All statistical calculations were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Autologous HCT

Demographics

Table 1 summarizes demographic data for the patients undergoing autologous HCT for AID. Ten of 53 centers registered with the CIBMTR reported 80% of the cases (n = 238). Thirty-six centers reported

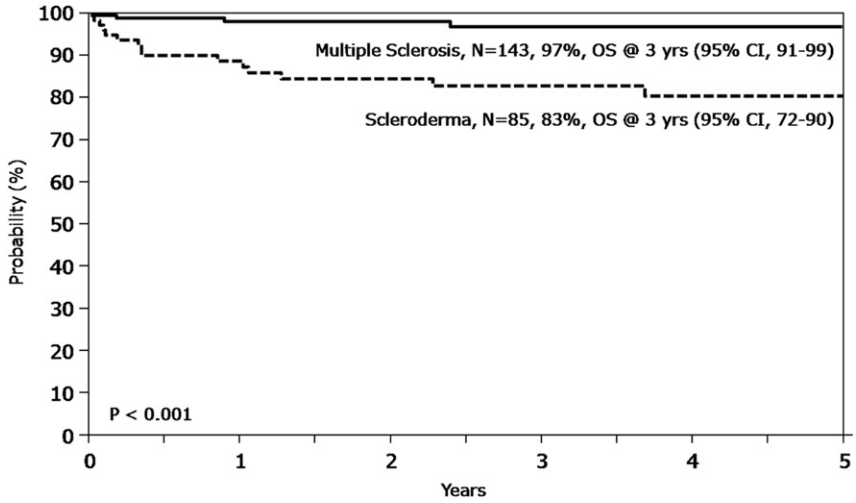

Figure 2. Overall survival, autologous HCT for multiple sclerosis and scleroderma.

fewer than 5 cases per center during the study period. The most common indication for HCT was MS (n = 143), followed by SSC (n = 85) and then SLE (n = 27). The number of HCTs per year increased rapidly from 1996 to 2001 and peaked in 2005 at 41. Between 2002 and 2009, 20 to 40 autologous HCTs per year were reported to the CIBMTR. Figure 1 outlines HCT activity by disease. A conditioning regimen that included cyclophosphamide plus antithymocyte globulin (ATG) with or without total body irradiation was used in most patients. The majority of grafts used granulocyte colony-stimulating factor–mobilized blood cells.

Among the 93 of 149 patients with MS with available data on disease subtype, 62 (67%) had secondary progressive MS, 23 (25%) had primary progressive MS, and 8 (8%) had relapsing remitting MS at the time of HCT. Among the 62 patients with available pretransplantation Expanded Disability Status Scale data, the median score was 6.5 (range, 3.0-8.0).

Survival

Thirty-eight recipients of autologous HCT died, with 26 considered treatment-related deaths. Causes of death were AID (n = 11), other infections (n = 9), organ failure (n = 5), bleeding (n = 5), cancer (n = 2), myelodysplasia (n = 1), graft failure (n = 1), thrombotic thrombocytopenic purpura ([TTP] n = 1), and unknown (n = 3). Table 2 summarizes the causes of death by indication for HCT. Median follow-up duration for all survivors after autologous HCT was 31 months (range, <1-144 months). The probabilities of survival were 93% (95% confidence interval [CI], 90%-96%) at 1 year and 86% (95% CI, 81%-91%) at 3 years. One-year and 3-year survival rates for patients with MS were 98% (95% CI, 94%-99%) and 97% (95% CI, 91%-99%), respectively. Corresponding probabilities for patients with SSC were 90% (95% CI, 80%-95%) and 83% (95% CI, 72%-90%) (Figure 2).

Results of multivariate analysis of prognostic factors for mortality after autologous HCT for AID are summarized in Table 3. Mortality was higher in patients from centers that performed 15 or fewer autologous HCTs for AID during the study period compared with patients from centers that performed more than 15 autologous HCTs for this indication.

Table 3. Multivariate Analysis for Overall Mortality after Autologous HCT for AID

	Number of Patients	Number of Centers	Relative Risk	95% CI	*P* Value
HCTs for AID/center*					.023†
>15	160	4	1.0	–	–
5-15	83	13	4.2	1.5-11.7	.006
<5	52	36	3.5	1.1-11.1	.035
Disease					.10†
MS	143	–	1.0	–	–
SSC	81	–	1.7	0.7-4.0	.18
SLE	23	–	2.8	1.0-7.5	.04
Other	48	–	0.5	0.1-2.8	.48

*Number of HCTs for AID/center performed during the study period.
†Overall *P* value for the covariate, HCT for AID/center with 2 degrees of freedom, disease with 3 degrees of freedom.

Allogeneic HCT

Table 4 summarizes data for 29 patients undergoing allogeneic HCT for AID. The most common indication was SSC (n = 15), followed by autoimmune cytopenias (n = 8). The median age of recipients was 25 years (range, 3-54 years). Diverse donor and graft types, graft-versus-host disease prophylaxis regimens, and conditioning regimens were used. Median follow-up of survivors of allogeneic HCT was 24 months (range, <1-107 months). One-year overall survival was 58% (95% CI, 38%-73%). Causes of death after allogeneic HCT were infection (n = 3), idiopathic pneumonia (n = 3), organ failure (n = 2), TTP (n = 1), bleeding (n = 1), and unknown (n = 1).

Table 4. Characteristics of Recipients of Allogeneic HCT for Treatment of AID

Disease Indication	Year	Age, Years	Donor	Graft	Conditioning/GVHD Prophylaxis	Follow-Up, Months	Status (Cause of Death)
SSC	1999	38	MSD	BM	Bu + Cy/MTX + CSA	60	Alive
	2000	19	MSD	PB	Cy + ATG/MTX + Tacro	55	Alive at last follow-up
	2001	20	MRD	BM	Cy + TLI/CSA	58	Alive at last follow-up
	2004	45	MSD	PB	Cy + ATG/CSA	36	Alive at last follow-up
	2004	54	MSD	PB	Cy + ATG/MTX + Tacro	30	Alive at last follow-up
	2004	28	MSD	PB	Cy + ATG/MTX + Tacro	7	Dead (unknown)
	2007	10	MUD	CB	Bu + Flu + Campath/Tacro + MMF	1	Alive at last follow-up
	2008	25	MSD	PB	Cy + TLI/other	–	Alive at last follow-up
	2008	16	MUD	CB	Cy + TBI/MTX + Tacro	2	Alive at last follow-up
	2009	22	MUD	CB	Flu + Cy + TBI + ATG/MMF + Tacro	13	Alive at last follow-up
	2009	52	MUD	CB	Flu + Cy + TBI + ATG/MMF + Tacro	1	Dead (IPN)
	2009	45	MUD	CB	Flu + Cy + TBI + ATG/MMF + Tacro	0	Dead (IPN)
	2009	11	MSD	BM	Flu + Mel + Campath/MTX + Tacro	2	Dead (organ failure)
	2009	17	MUD	CB	Flu + Mel + Campath/MTX + Tacro	0	Dead (TTP)
	2009	61	MSD	PB	Cy + Flu + Campath/MMF	1	Dead (infection)
Evans syndrome	1998	3	MUD	BM	Bu + ATG/CSA + corticosteroid	107	Alive at last follow-up
	2003	12	MUD	CB	Flu + Mel + Campath/MTX + CSA	3	Dead (IPN)
	2005	6	MUD	BM	Bu + Flu + Campath/MTX + CSA	<1	Dead (hemorrhage)
	1998	36	MSD	BM	BCNU + ATG/ MTX + CSA	<1	Dead (organ failure)
Hemolytic anemia	2005	8	MUD	CB	Cy + TBI/Tacro/MMF	12	Alive at last follow-up
Autoimmune cytopenia	2007	6	MSD	BM	Cy + other/MTX + CSA	3	Alive at last follow-up
ITP	2006	37	MUD	BM	Cy + ATG + TBI/CSA + MMF	49	Alive at last follow-up
	2007	15	MSD	BM	ATG + BU + CY/MTX + Tacro	24	Alive at last follow-up
SLE	2000	10	MSD	BM	Bu + ATG	<1	Dead (infection)
	2003	41	MSD	PB	TLI + ATG/CSA + MMF	36	Alive at last follow-up
	2007	53	MSD	PB	ATG + TLI/CSA + MMF	24	Alive at last follow-up
AID, other	2000	9	MSD	BM	Bu + Cy/T cell depletion	<1	Alive at last follow-up
	2005	20	MUD	PB	Cy + TBI/MTX + CSA	<1	Dead (infection)
Myasthenia gravis	2005	14	MSD	PB	Bu + Flu + Campath/MTX + CSA	11	Alive at last follow-up

ATG indicates antithymocyte globulin; BCNU, carmustine; BM, bone marrow; Bu, busulfan; CSA, cyclosporine A; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; IPN, idiopathic pneumonia syndrome; ITP, idiopathic thrombocytopenia purpura; Mel, melphalan; MMF, mycophenolate mofetil; MSD, matched sibling donor; MUD, matched unrelated donor; MTX, methotrexate; PB, mobilized peripheral blood stem cells; Tacro, tacrolimus; TBI, total body irradiation; TLI, total lymphoid irradiation.

DISCUSSION

We report HCT activity for patients with AID in the Americas. Examination of the patient-to-center ratio indicates that HCTs for AID are rare compared with HCTs for other indications, with only 8 of 47 active CIBMTR centers reporting more than 10 cases. Importantly, we found a significant center effect related to the number of HCTs performed for AID. Patients at centers performing 15 or fewer autologous HCTs for AID had a higher risk of death than those at centers performing more than 15 HCTs. This may be related to participation of centers with higher volumes in clinical trials of HCT for AID and established programs with cross-specialty collaboration, whereas centers with a low HCT volume for these indications may perform transplantation on a compassionate basis for patients with severe AID.

Reporting autologous HCTs to the CIBMTR is voluntary, and these data do not encompass all activity in the region. Published data and surveys of centers indicate that although most HCTs for AID in Canada and Brazil are reported, there may be at least 250 additional cases in the United States during the period of this study [30]. The breakdown of indications for those 250 cases is likely similar to the data reported here, with the most common indication being MS, followed by SSC, SLE and autoimmune cytopenias [8,28,30-37]. The European Group for Blood and Marrow Transplantation has reported almost 1,300 HCTs performed for AID in Europe [10,38]. The most common indications in the European data are MS, SSC, and SLE, similar to our data. One exception is the higher number of HCTs for diabetes mellitus reported in Brazil (n = 22). Other AID indications for HCT that were once relatively common, such as rheumatoid arthritis and juvenile idiopathic arthritis, are now rare. This is likely because of the availability of more effective nontransplantation therapies and unsatisfactory HCT outcomes for arthritis.

Our data indicate that survival was correlated with type of AID, with the best outcomes in patients with MS. Three-year mortality in these patients in our series was <5%, similar to data in the literature [11]. Previous studies have reported significant reductions in transplantation-related mortality after autologous HCT for MS in recent years, with lower rates with the use of less-intensive conditioning regimens [31,33,39,40]. However, transplantation-related mortality remains a significant concern, given the significant comorbidities in patients with AID.

Despite encouraging long-term clinical results in selected patients with generally severe and otherwise refractory AID, the role of HCT for AID remains to

be evaluated in randomized clinical trials [23]. The low number of HCTs for AID in the Americas compared with Europe reflects barriers and a reluctance to use this therapy broadly and makes conducting comparative trials very difficult.

Another concern regarding the use of HCT for AID is the high cost of this procedure. Third-party payers in the United States are often reluctant to cover this therapy [41]. However, the newer biological agents now being used to treat AID are also costly and require chronic use. Sparing patients from chronic immunosuppressive therapy may be an important outcome of HCT, avoiding the side effects now emerging with biological therapies [42-44]. Preliminary analyses indicate that HCT indeed might be cost-effective in some situations [45], but further research is needed.

Allogeneic HCT for AID is performed less commonly than autologous HCT. The greater morbidity and mortality rates with graft-versus-host disease are clear barriers to this therapy; however, complete elimination and replacement of a patient's own immune system may be a desirable goal. Pilot studies in SSC have shown resolution of disease manifestations [17].

The present study is limited by a lack of disease-specific response data. Although the CIBMTR requests these data, transplantation centers face substantial financial and logistical challenges in complying with this requirement. Most posttransplantation care is provided by AID specialists, and it is common for patients to return to the transplant center only rarely, if ever. Current efforts at CIBMTR are aimed at increasing reporting of disease-specific outcomes [46,47].

Ultimately, only direct comparisons of HCT with nontransplantation therapies by means of comparative trials will allow evaluation of the relative efficacy and role of HCT in AID. Outcomes registries can be helpful in planning such trials by identifying the patients most likely to benefit, the regimens most likely to be effective, late effects of transplantation, and the outcomes most likely to be affected.

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APPENDIX: CONTRIBUTING CENTERS

Center	City	Country
Albert Einstein Hospital	São Paulo	Brazil
Barnes Jewish Hospital	St Louis	United States
Baylor College	Houston	United States
British Columbia's Children's Hospital, University of British Columbia	Vancouver	Canada
British Hospital	Montevideo	Uruguay
Cancer Care Manitoba/University of Manitoba	Winnipeg	Canada
Cardinal Glennon Children's Medical Center	St Louis	United States
Centre Hospitalier	Montreal	Canada
Children's Hospital of Philadelphia	Philadelphia	United States
Children's National Medical Center	Washington	United States
Cincinnati Children's Hospital Medical Center	Cincinnati	United States
Dartmouth-Hitchcock Medical Center	Lebanon	United States
Duke University Medical Center	Durham	United States
Emory University Hospital	Atlanta	United States
Fred Hutchinson Cancer Center	Seattle	United States
Froedtert Memorial Lutheran Hospital	Milwaukee	United States
Hospital de Clinicas–UFPR	Curitiba	Brazil
Hospital of the University of Pennsylvania	Philadelphia	United States
Hospital Rebagliati	Lima	Peru
Johns Hopkins Oncology Center	Baltimore	United States
Karmanos Cancer Institute, Wayne State University	Detroit	United States
Loma Linda University Medical Center	Loma Linda	United States
M.D. Anderson Cancer Research Center	Houston	United States
Massachusetts General Hospital	Boston	United States
Mayo Clinic Rochester	Rochester	United States
Mcgill University Health Center	Montreal	Canada
Medical University of South Carolina	Charleston	United States
Morgan Stanley Children's Hospital of New York	New York	United States
Mount Sinai Medical Center	New York	United States
National Cancer Institute	Rockville	United States
NYPH/ Columbia University Medical Center	New York	United States
The Ottawa Hospital	Ottawa	Canada
Penn State Milton S. Hershey Medical Center	Hershey	United States
Princess Margaret Hospital	Toronto	Canada
Rady Children's Hospital	San Diego	United States
Real Hospital Portugues	Recife	Brazil
Scripps Clinic Research Foundation	San Diego	United States
Shands HealthCare and University of Florida	Gainesville	United States
Stanford University Medical Center	San Francisco	United States
Texas Transplant Institute	Dallas	United States
The Nebraska Medical Center	Omaha	United States
The Ohio State University Medical Center	Columbus	United States
The University of Michigan	Ann Arbor	United States
Thomas Jefferson University	Philadelphia	United States
Tom Baker Cancer Centre/University of Calgary	Calgary	Canada
Tulane University Medical Center	New Orleans	United States
UNICAMP – HEMOCENTRO	Campinas	Brazil
Universidade de Sao Paulo	Ribeirão Preto	Brazil
University of Arizona Health Sciences Center	Phoenix	United States
University of California San Francisco Medical Center	San Francisco	United States
University of California-San Diego	San Diego	United States
University of Chicago Hospitals	Chicago	United States
University of Iowa Hospital and Clinics	Iowa City	United States
University of Kansas	Kansas City	United States
University of Massachusetts Memorial Medical Center	Boston	United States
University of Pittsburgh Cancer Center	Pittsburg	United States
University of Utah	Salt Lake City	United States
University of Wisconsin Hospital and Clinics	Madison	United States
USAF Wilford Hall Medical Center	Lackland Air Force Base	United States
VA Puget Sound Health Care System	Seattle	United States
Washington University/St Louis Children's Hospital	St Louis	United States