Significant Improvement in Survival After Allogeneic Hematopoietic Cell Transplantation During a Period of Significantly Increased Use, Older Recipient Age, and Use of Unrelated Donors

Theresa Hahn, Philip L. McCarthy Jr, Anna Hassebroek, Christopher Bredeson, James L. Gajewski, Gregory A. Hale, Luis M. Isola, Hillard M. Lazarus, Stephanie J. Lee, Charles F. LeMaistre, Fausto Loberiza, Richard T. Maziarz, J. Douglas Rizzo, Steven Joffe, Susan Parsons, and Navneet S. Majhail

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on May 28, 2013.

Presented in part at the 52nd Annual Meeting of the American Society of Hematology, Orlando, FL, December 4-7, 2010, and Tandem Meeting of the American Society of Blood and Marrow Transplantation and Center for International Blood and Marrow Transplant Research, Orlando, FL, February 24-28, 2010.

The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, Department of the Navy, Department of Defense, or any other agency of the US Government.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Navneet S. Majhail, MD, MS, National Marrow Donor Program, 3001 Broadway Ave NE, Suite 100, Minneapolis, MN 55413; e-mail: nmajhail@nmdp.org.

© 2013 by American Society of Clinical Oncology

0732-183X/13/3119w-2437w/\$20.00

DOI: 10.1200/JCO.2012.46.6193

ABSTRACT

Purpose

Over the past four decades, allogeneic hematopoietic cell transplantation (alloHCT) has evolved as a curative modality for patients with hematologic diseases. This study describes changes in use, technique, and survival in a population-based cohort.

Patients and Methods

The study included 38,060 patients with hematologic malignancies or disorders who underwent first alloHCT in a US or Canadian center from 1994 to 2005 and were reported to the Center for International Blood and Marrow Transplant Research.

Results

AlloHCT as treatment for acute lymphoblastic (ALL) and myeloid leukemias (AML), myelodysplastic syndrome (MDS), and Hodgkin and non-Hodgkin lymphomas increased by 45%, from 2,520 to 3,668 patients annually. From 1994 to 2005, use of both peripheral (7% to 6%) and cord blood increased (2% to 10%), whereas use of marrow decreased (90% to 27%). Despite a median age increase from 33 to 40 years and % increase in unrelated donors for alloHCT, overall survival (OS) at day 100 significantly improved for patients with AML in first complete remission after myeloablative sibling alloHCT (85% to 94%; $P < .001$) and unrelated alloHCT (63% to 86%; $P < .001$); 1-year OS improved among those undergoing unrelated alloHCT (48% to 63%; $P = .003$) but not among those undergoing sibling alloHCT. Similar results were seen for ALL and MDS. Day-100 OS after cord blood alloHCT improved significantly from 60% to 78% ($P < .001$) for AML, ALL, MDS, and chronic myeloid leukemia. Use of reduced-intensity regimens increased, yielding OS rates similar to those of myeloablative regimens.

Conclusion

Survival for those undergoing alloHCT has significantly improved over time. However, new approaches are needed to further improve 1-year OS.

J Clin Oncol 31:2437-2449. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is a curative modality for selected patients with hematologic malignancies, nonmalignant hematologic disorders, immunodeficiencies, and genetic disorders (ie, storage diseases and hemoglobinopathies). Over the past four decades, the practice of alloHCT has evolved, with new sources of hematopoietic cells (peripheral blood and umbilical cord blood [UCB]),¹ the advent of reduced-intensity and nonmyeloablative conditioning regimens that provide a curative option to patients who otherwise would not have undergone alloHCT in

the past,²⁻⁶ the introduction of tacrolimus and mycophenolate mofetil for graft-versus-host disease (GVHD) prophylaxis,^{7,8} higher resolution and number of loci tested for HLA matching,⁹ and increased number and ethnic diversity of the unrelated-donor pool.^{10,11} The latter two have improved donor HLA matching and selection. Simultaneously, there have been major changes to cancer treatments, with the development of monoclonal antibodies (rituximab, alemtuzumab), tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib), immunomodulatory drugs (thalidomide, lenalidomide), small-molecule inhibitors (bortezomib, sirolimus, temsirolimus, everolimus), hypomethylating agents

(azacitidine, decitabine), and other novel therapies. These changing treatment paradigms may have affected referral patterns and indications for alloHCT.¹² In addition, several nonmedical practices have affected alloHCT referrals (eg, varying insurance coverage of alloHCT for multiple myeloma [MM] and myelodysplastic syndrome [MDS]).¹³⁻¹⁶

The existence of the Center for International Blood and Marrow Transplant Research (CIBMTR), a worldwide registry of alloHCT, makes it possible to study whether and how the use of alloHCT in the therapy of cancer and other disorders has changed over time. The study reported herein describes the changes in the alloHCT patient population and their overall survival (OS) rates over a 12-year period.

PATIENTS AND METHODS

About the CIBMTR

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and National Marrow Donor Program (NMDP). Established in 2004, it comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive alloHCTs and autologous HCTs to a statistical center at the Medical College of Wisconsin (Milwaukee, WI) and the NMDP Coordinating Center (Minneapolis, MN). The International Bone Marrow Transplant Registry has been collecting alloHCT data from centers worldwide since 1972, and the Autologous Blood and Marrow Transplant Registry has collected autologous HCT data from centers in North and South America since 1991. Participating centers are required to report all transplantations consecutively; compliance is monitored by onsite audits. Patients are observed longitudinally. Computerized checks for discrepancies, physician review of submitted data, and onsite audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed under the guidance of the institutional review boards of the Medical College of Wisconsin and the NMDP and are in compliance with all applicable federal regulations pertaining to the protection of human research participants.

Study Population

For this study, we selected first alloHCTs performed in the United States or Canada and reported to the CIBMTR between 1994 and 2005. Our final study population consisted of 38,060 patients undergoing first alloHCT performed in the United States or Canada from 1994 to 2005.

Data Collection and Reporting

During the study period, 286 unique transplantation centers contributed data to the CIBMTR. During each of the 12 years in the study period, 109 centers (38%) reported at least one alloHCT to the CIBMTR. Only 70 centers (24%) provided data for less than half of the study period.

The CIBMTR collects data at two levels: transplant-essential data (TED) and comprehensive report form (CRF) data. TED include disease type, age, sex, pretransplantation disease stage and chemotherapy responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, post-transplantation disease progression and survival, development of new malignancy, and cause of death. All CIBMTR teams contribute TED. More detailed disease and pre- and post-transplantation clinical information are collected for a subset of registered patients selected for CRF data by a weighted randomization scheme. TED and CRF data are collected before transplantation, 100 days and 6 months after transplantation, and annually thereafter or until death.

For the purpose of this study, to obtain the broadest representation of alloHCT use, CIBMTR TED were used. HLA match was defined by the individual center and varied over time in response to changes in HLA typing during the study period.⁹ Karnofsky (KPS)/Lansky performance score was reported as < 80 or ≥ 80.

Statistical Analysis

The cohort was divided into six 2-year time periods to permit description of trends over time. Descriptive statistics, including proportions, medians, and ranges, were calculated. There were no tests of statistical significance for volume data. OS estimates and 95% CIs were calculated at day +100, which primarily represents early transplantation-related mortality (TRM), and at 1 year, which represents disease-related mortality and later TRM. Statistical significance was measured using pointwise *P* values. OS estimates were determined for a priori defined disease and disease status subgroups and were not adjusted for any patient or disease covariates. Disease status subgroups with significant trends in OS over time were stratified by age to determine the pattern of OS trend by age. To reduce type I error, *P* < .01 was considered statistically significant.

Estimation of the Rate of AlloHCT Over Time

Age-specific incidence of six major hematologic disorders (acute lymphoblastic leukemia [ALL], acute myeloid leukemia [AML], Hodgkin lymphoma [HL], non-Hodgkin lymphoma [NHL], MM, and MDS) was obtained from the National Cancer Institute SEER database from 1994 to 2005.¹⁷ Age-specific intercensal population estimates from 1994 to 2005 were obtained from the US Census Bureau.¹⁸ The number of new patient cases of each disease by age group and year was estimated by applying the age-specific SEER incidence to the US national population in that age group. AlloHCTs for these six major hematologic disorders were actual numbers reported to the CIBMTR that captured approximately 70% to 90% of related-donor and 90% of unrelated-donor alloHCTs performed at a US transplantation center during the period of 1994 to 2005. Therefore, an inflation factor of 1.11 was applied to the reported unrelated-donor alloHCTs and an inflation factor of 1.15 to 1.43 was applied to the reported related-donor alloHCTs to account for variances in the proportion of all alloHCTs performed in the United States that were reported to the CIBMTR. The rate of alloHCT for each disease was calculated by dividing the number of alloHCTs (after applying the inflation factor) by the number of newly diagnosed patients, excluding incident patient cases and alloHCTs for those age ≥ 75 years and excluding alloHCTs performed in Canada.

RESULTS

Patient Characteristics

Characteristics of patients who underwent alloHCT are summarized in Table 1. Each of the 2-year cohorts experienced an increase in alloHCT volume over the prior 2-year cohort. The number of transplantation centers with active reporting in any 2-year period ranged from 143 to 161. Median age increased over the study period (from 33 years in 1994 to 1995 to 40 years in 2004 to 2005). Although the number of patients undergoing alloHCT age ≥ 60 years increased, these patients comprise only 10% of all alloHCTs performed. There was improvement in the collection of KPS over the entire study period, with 47% missing data in the period of 1994 to 1995 and 13% missing data in the period of 2004 to 2005. Because of the large amount of incomplete data on KPS for most of the study period, it was difficult to assess changes in patient characteristics over time. Similarly, between 1997 and 1998, there was improvement in completeness of data collected for race. Since 1998, the proportion of alloHCTs for nonwhite races/ethnicities remained stable. The number of alloHCTs performed in Canada increased by > 75% between 1994 to 1995 and 2004 to 2005.

Disease Indications and Transplantation Types

A majority of alloHCTs performed in 1994 to 1995 were for AML (25%), chronic myeloid leukemia (CML; 23%), and ALL (18%). Since 2000, there has been a decrease in the number of alloHCTs performed

Increased Use of and Improved Survival After AlloHCT

Table 1. Characteristics of Patients From the United States and Canada Who Underwent and Registered Allogeneic Transplantation to CIBMTR, 1994 to 2005

Characteristic	1994 to 1995		1996 to 1997		1998 to 1999		2000 to 2001		2002 to 2003		2004 to 2005	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	5,053		6,160		6,403		6,421		6,686		7,337	
No. of centers	143		151		157		161		162		161	
Age, years												
Median	33		35		37		39		40		40	
Range	< 1 to 68		< 1 to 79		< 1 to 76		< 1 to 79		< 1 to 76		< 1 to 78	
< 1 to 9	825	16	1,009	16	924	14	949	15	1,031	15	1,107	15
10 to 19	666	13	755	12	739	12	719	11	792	12	916	12
20 to 29	662	13	732	12	749	12	666	10	632	9	726	10
30 to 39	1,097	22	1,137	18	1,166	18	972	15	856	13	823	11
40 to 49	1,217	24	1,556	25	1,553	24	1,491	23	1,420	21	1,339	18
50 to 59	517	10	842	14	1,083	17	1,241	19	1,393	21	1,707	23
60 to 69	43	1	96	2	170	3	358	6	521	8	675	9
≥ 70	0	0	7	< 1	13	< 1	18	< 1	41	1	42	1
Missing	26	1	26	< 1	6	< 1	7	< 1	0	0	2	< 1
Sex												
Male	2,965	59	3,567	58	3,727	58	3,758	59	3,993	60	4,338	59
Missing	7	< 1	1	< 1	31	< 1	29	< 1	12	< 1	8	< 1
Karnofsky/Lansky performance score												
≥ 80	2,397	47	2,572	42	2,346	37	4,354	68	4,958	74	5,888	80
< 80	275	5	328	5	289	5	464	7	559	8	498	7
Missing	2,381	47	3,260	53	3,768	59	1,603	25	1,169	17	951	13
Race												
White	3,102	61	3,994	65	4,860	76	4,908	76	5,072	76	5,616	77
African American	260	5	384	6	496	8	458	7	467	7	493	7
Asian/Pacific Islander	115	2	148	2	209	3	192	3	184	3	242	3
Hispanic	237	5	410	7	502	8	492	8	423	6	283	4
Other	96	2	98	2	125	2	133	2	220	3	385	5
Missing	1,243	25	1,126	18	211	3	238	4	320	5	318	4
Country												
United States	4,599	91	5,614	91	5,882	92	5,727	89	5,899	88	6,537	89
Canada	454	9	546	9	521	8	694	11	787	12	800	11
Disease												
AML	1,278	25	1,456	24	1,649	26	1,791	28	2,026	30	2,478	34
ALL	892	18	985	16	897	14	1,021	16	1,049	16	1,218	17
MDS/MPS	398	8	526	9	544	8	585	9	705	11	833	11
Non-Hodgkin lymphoma	331	7	624	10	715	11	783	12	902	13	814	11
CML	1,175	23	1,339	22	1,411	22	883	14	608	9	552	8
CLL	68	1	120	2	138	2	195	3	268	4	319	4
Severe aplastic anemia	243	5	276	4	256	4	222	3	235	4	301	4
Inherited abnormalities of erythrocyte differentiation	71	1	92	1	97	2	118	2	151	2	174	2
Immune deficiencies	107	2	146	2	152	2	110	2	143	2	155	2
Metabolic disorders	73	1	86	1	91	1	122	2	122	2	130	2
Hodgkin lymphoma	42	1	67	1	76	1	74	1	69	1	84	1
Other leukemia	64	1	64	1	63	1	55	1	69	1	73	1
MM	234	5	261	4	176	3	189	3	140	2	71	1
Solid tumor	24	< 1	50	1	90	1	189	3	136	2	68	1
Other	39	1	61	1	45	1	68	1	63	1	66	1
Missing	14	< 1	7	< 1	3	< 1	16	< 1	0	0	1	< 1
Disease status pretransplantation												
AML												
CR1	491	38	527	26	575	35	671	37	805	40	1,023	41
≥ CR2	196	15	252	17	307	19	355	20	397	20	571	23
Relapse/primary induction failure	470	37	573	39	653	40	615	34	616	30	637	26
Other/unknown/missing	121	9	104	7	114	7	150	8	208	10	247	10

(continued on following page)

Table 1. Characteristics of Patients From the United States and Canada Who Underwent and Registered Allogeneic Transplantation to CIBMTR, 1994 to 2005 (continued)

Characteristic	1994 to 1995		1996 to 1997		1998 to 1999		2000 to 2001		2002 to 2003		2004 to 2005	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
ALL												
CR1	247	28	270	27	235	26	300	29	333	32	429	35
≥ CR2	395	44	446	45	403	45	447	44	477	45	551	45
Relapse/primary induction failure	197	22	220	22	224	25	226	22	183	17	170	14
Other/unknown/missing	53	6	49	5	35	4	48	5	56	5	68	6
CML												
First chronic phase	798	68	908	68	935	66	578	65	314	52	312	57
≥ Second chronic phase	35	3	46	3	93	7	65	7	86	14	73	13
Accelerated phase/blastic phase	231	20	282	21	277	20	168	19	164	27	124	22
Other/unknown/missing	111	9	103	8	106	8	72	8	44	7	43	8
MDS/MPS												
Refractory anemia ± ringed sideroblasts	60	15	85	16	91	17	99	17	131	19	149	18
Refractory anemia with excess blasts ± transformation	152	38	226	43	199	37	203	35	233	33	277	33
Other/unknown/missing	186	47	215	41	254	47	283	48	341	48	407	49
Non-Hodgkin lymphoma												
CR2/first chemosensitive relapse	78	24	117	19	168	24	167	21	222	25	204	25
CR1	32	10	44	7	52	7	60	8	77	9	99	12
CR3/≥ second chemosensitive relapse	16	5	42	7	56	8	77	10	114	13	120	15
Other/unknown/missing	205	62	421	67	439	61	479	61	489	54	391	48
Hodgkin lymphoma												
CR2/first chemosensitive relapse	9	21	12	18	16	21	15	20	16	23	14	17
CR1	0	0	0	0	3	4	4	5	4	6	4	5
≥ CR3/≥ second chemosensitive relapse	3	7	7	10	9	12	11	15	8	12	8	10
Other/unknown/missing	30	71	48	72	48	63	44	59	41	59	58	69
MM												
CR1 or first partial remission	43	18	63	24	49	28	79	42	67	48	32	45
Other*	124	53	120	46	67	38	67	35	52	37	27	38
Unknown/missing	67	29	78	30	60	34	43	23	21	15	12	17
Time from diagnosis to transplantation, months												
Median	8		9		8		9		9		9	
Range	< 1 to 532		< 1 to 560		< 1 to 653		< 1 to 585		< 1 to 476		< 1 to 674	
< 12	2,944	58	3,466	56	3,691	58	3,639	57	3,662	55	4,029	55
12 to 23	831	16	1,090	18	1,135	18	1,163	18	1,208	18	1,330	18
24 to 35	357	7	488	8	452	7	485	8	551	8	600	8
≥ 36	721	14	897	15	945	15	973	15	1,173	18	1,320	18
Missing	200	4	219	4	180	3	161	3	92	1	58	1
Donor type												
HLA-identical sibling	2,999	59	3,566	58	3,593	56	3,466	54	3,410	51	3,263	44
Other relative	621	12	633	10	585	9	596	9	496	7	526	7
Unrelated	1,237	24	1,804	29	2,039	32	2,187	34	2,616	39	3,274	45
Other	25	< 1	18	< 1	20	< 1	61	1	87	1	160	2
Missing	171	3	139	2	166	3	111	2	77	1	114	2
Sex match (donor/recipient)												
Male donor, male recipient	878	17	876	14	870	14	1,807	28	2,255	34	2,502	34
Male donor, female recipient	564	11	578	9	538	8	1,093	17	1,358	20	1,562	21
Female donor, male recipient	697	14	692	11	654	10	1,276	20	1,525	23	1,663	23
Female donor, female recipient	556	11	610	10	515	8	1,059	16	1,198	18	1,321	18
Other/missing	2,358	47	3,404	55	3,826	60	1,186	18	350	5	289	4
Graft source												
Peripheral blood	357	7	1,139	18	1,682	26	3,020	47	3,912	59	4,588	63
Bone marrow	4,571	90	4,696	76	4,260	67	2,842	44	2,111	32	1,970	27
Cord blood	85	2	281	5	407	6	531	8	652	10	752	10
Bone marrow and peripheral blood	40	1	44	1	54	1	28	< 1	11	< 1	27	< 1
Conditioning intensity												
Ablative	5,053	100	5,813	94	5,516	86	5,043	79	4,900	73	5,260	72
Reduced intensity/nonmyeloablative	0	0	88	1	416	6	1,165	18	1,689	25	2,000	27
Missing	0	0	259	4	471	7	213	3	97	1	77	1

(continued on following page)

Table 1. Characteristics of Patients From the United States and Canada Who Underwent and Registered Allogeneic Transplantation to CIBMTR, 1994 to 2005 (continued)

Characteristic	1994 to 1995		1996 to 1997		1998 to 1999		2000 to 2001		2002 to 2003		2004 to 2005	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Conditioning regimen												
Cy + TBI ± other	2,194	43	2,675	43	2,758	43	2,310	36	2,206	33	2,224	30
Bu + Cy ± other	1,484	29	1,822	30	1,864	29	1,278	20	1,435	21	1,646	22
TBI ± other (no Cy)	287	6	400	6	399	6	539	8	567	8	669	9
Cy ± other	306	6	386	6	428	7	472	7	575	9	585	8
Fludarabine + melphalan ± ATG	0	0	1	< 1	47	1	166	3	171	3	328	4
Bu + fludarabine	0	0	0	0	22	< 1	126	2	226	3	325	4
Bu + fludarabine + ATG ± other	1	< 1	4	< 1	58	1	216	3	264	4	275	4
Bu + melphalan ± ATG	7	< 1	30	< 1	51	1	54	1	58	1	64	1
BEAM	4	< 1	31	1	45	1	21	< 1	27	< 1	30	< 1
Melphalan	3	< 1	6	< 1	15	< 1	15	< 1	12	< 1	10	< 1
None	24	< 1	32	1	20	< 1	12	< 1	15	< 1	17	< 1
Other	424	8	547	9	521	8	301	5	353	5	415	6
Missing	319	6	226	4	175	3	911	14	777	12	749	10
GVHD prophylaxis												
Tacrolimus + methotrexate	54	1	102	2	366	6	918	14	1,552	23	2,060	28
Cyclosporine + methotrexate ± other	2,427	48	3,005	49	2,764	43	1,954	30	1,799	27	1,695	23
Cyclosporine ± other (no methotrexate)	819	16	1,041	17	986	15	1,226	19	1,370	20	1,317	18
Tacrolimus based (no methotrexate)	66	1	71	1	77	1	175	3	440	7	826	11
T-cell depletion	900	18	783	13	815	13	639	10	359	5	358	5
Methotrexate alone	226	4	320	5	564	9	226	4	195	3	157	2
None	104	2	112	2	176	3	231	4	154	2	150	2
Other	93	2	382	6	226	4	48	1	54	1	51	1
Missing	364	7	344	6	429	7	1,004	16	763	11	723	10
Type of second transplantation												
One transplantation only	4,677	93	5,682	92	5,909	92	5,891	92	6,084	91	6,832	93
Two transplantations, both allogeneic	360	7	469	8	481	8	525	8	594	9	489	7
Missing	16	< 1	9	< 1	13	< 1	5	< 1	8	< 1	16	< 1

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; BEAM, nitrosourea, etoposide, cytarabine, and melphalan; Bu, busulfan; CIBMTR, Center for International Blood and Marrow Transplant Research; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CR1, first complete remission; CR2, second complete remission; CR3, third complete remission; Cy, cyclophosphamide; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPS, myeloproliferative disorder; TBI, total body irradiation.

*Other includes minimal response, no response/stable disease, progression/relapse, and ≥ CR2.

for CML (from a peak of 1,411 in 1998 to 1999 to 552 in 2004 to 2005) and MM (from a peak of 261 in 1996 to 1997 to 71 in 2004 to 2005). Between 1994 to 1995 and 2004 to 2005, the number of alloHCTs doubled (or > doubled) for AML (1,278 to 2,478), MDS and myeloproliferative disease (398 to 833), NHL (331 to 814), chronic lymphocytic leukemia (68 to 319), inherited abnormalities of erythrocyte differentiation (71 to 174), HL (42 to 84), and solid tumors (24 to 68). Over time, there has been a shift in patients with CML treated with alloHCT from first chronic phase (early-stage disease) to ≥ second chronic phase (intermediate-stage disease); however, the remaining indications for alloHCT demonstrated stability in disease stage at time of alloHCT, with a corresponding proportion of patients undergoing transplantation within 12 months after diagnosis, which also remained stable (58% in 1994 to 1995; 55% in 2004 to 2005).

The number of HLA-identical sibling-donor alloHCTs ranged from a low of 2,999 in 1994 to 1995 to a peak of 3,593 in 1998 to 1999. Unrelated-donor alloHCTs ranged from a low of 1,237 in 1994 to 1995 to a peak of 3,274 in 2004 to 2005. Since 1994 to 1995, there has been a decrease in the number of grafts from bone marrow (4,571 in 1994 to 1995 to 1,970 in 2004 to 2005), with a corresponding increase in the number of grafts collected from peripheral blood (357 in 1994 to 1995 to 4,588 in 2004 to 2005) or UCB (85 in 1994 to 1995 to 752 in

2004 to 2005). The first reported reduced-intensity or nonmyeloablative conditioning regimen occurred during the period of 1996 to 1997, with 27% of alloHCTs in 2004 to 2005 using these regimens. Tacrolimus-based GVHD prophylaxis regimens also increased, from 120 in 1994 to 1995 to 2,886 in 2004 to 2005, with decreases in cyclosporine-based regimens (3,246 in 1994 to 1995 to 3,012 in 2004 to 2005) and T-cell depletion (900 to 358). The number of patients who underwent second unplanned alloHCT was relatively stable, ranging between 360 and 594 in any 2-year cohort.

Use of AlloHCT Over Time

The rate of alloHCT over time is summarized in Table 2. The US population age 0 to 74 years increased by 10.6% between 1994 and 2005. For AML, the incident rate in those age 0 to 74 years decreased by 10%, whereas the number of incident patient cases increased by 2%, and the rate of alloHCT for AML increased by 56% over this time, from 12.4% to 19.3%. For ALL, the incident rate in those age 0 to 74 years increased by 14%, and the number of incident patient cases increased by 18%, with a relatively stable rate of alloHCT for ALL at 12.3% to 13.8%. For NHL, the incident rate remained stable, and the number of incident patient cases increased by 10.3%, which corresponds to the increase in the US population; however, the rate of

Table 2. Changes Over Time in the US Population, Incident Patient Cases, and Proportion of Patients Who Underwent AlloHCT

Variable	1994 to 1995	1996 to 1997	1998 to 1999	2000 to 2001	2002 to 2003	2004 to 2005
Total US population (age 0 to 74 years), millions	249.9	255.5	261.2	266.8	271.6	276.5
AML						
Incidence rate per 100,000 persons	5.2	5.0	5.2	5.5	5.0	4.7
No. of new incident patient cases (age 0 to 74 years)	12,879	12,683	13,682	14,608	13,532	13,131
Rate of alloHCTs per new incident patient cases (age 0 to 74 years)	12.4%	12.4%	13.1%	13.0%	15.3%	19.3%
ALL						
Incidence rate per 100,000 persons	2.9	3.0	3.0	3.0	3.1	3.3
No. of new incident patient cases (age 0 to 74 years)	7706	7592	7926	8055	8404	9067
Rate of alloHCTs per new incident patient cases (age 0 to 74 years)	13.7%	13.8%	12.3%	13.6%	12.6%	13.6%
MDS/MPs						
Incidence rate per 100,000 persons	*	*	*	*	3.8	3.9
No. of new incident patient cases (age 0 to 74 years)	*	*	*	*	10,226	10,764
Rate of alloHCTs per new incident patient cases (age 0 to 74 years)	*	*	*	*	7.0%	7.8%
NHL						
Incidence rate per 100,000 persons	29.5	28.4	27.9	28.0	28.7	29.4
No. of new incident patient cases (age 0 to 74 years)	73,658	72,650	72,925	74,614	77,973	81,272
Rate of alloHCTs per new incident patient cases (age 0 to 74 years)	0.6%	1.0%	1.1%	1.1%	1.2%	1.0%
HL						
Incidence rate per 100,000 persons	5.1	5.2	5.3	5.1	5.2	5.3
No. of new incident patient cases (age 0 to 74 years)	12,787	13,330	13,856	13,707	14,212	14,706
Rate of alloHCTs per new incident patient cases (age 0 to 74 years)	0.4%	0.6%	0.7%	0.6%	0.5%	0.6%
MM						
Incidence rate per 100,000 persons	7.4	7.4	7.5	7.7	7.7	8.0
No. of new incident patient cases (age 0 to 74 years)	18,422	19,006	19,498	20,468	20,863	22,123
Rate of alloHCTs per new incident patient cases (age 0 to 74 years)	1.7%	1.5%	1.0%	1.0%	0.6%	0.3%

Abbreviations: ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; MM, multiple myeloma; MPS, myeloproliferative disorder; NHL, non-Hodgkin lymphoma.
 *SEER did not initiate data collection for MDS/MPD until 2001.

alloHCT for NHL increased by 66% during this time, from 0.6% to 1.0%. For HL, the incident rate increased by 4%; the number of incident patient cases increased by 15%, which exceeds the increase in the US population; and the rate of alloHCT for HL increased by 50% during this time, from 0.4% to 0.6%. For MM, the incident rate increased by 8%, and the number of incident cases increased by 20%, which exceeds the increase in the US population; however, the rate of alloHCT for MM decreased by 82% during this time, from 1.7% to 0.3%.

OS After HLA-Matched Sibling-Donor AlloHCT

In every disease group that received a myeloablative conditioning regimen, OS at 100 days after HCT demonstrated statistically significant increases over time (Table 3). In all age groups, OS estimates at day +100 after alloHCT in the most recent cohort (2004 to 2005) ranged from 88% in patients with MDS to 98% in patients with CML undergoing transplantation in first chronic phase. Even in older patients age 40 to 59 years at time of HCT, OS estimates at day +100 after alloHCT were 89% for those with AML in first complete remission (CR1), 84% for those with CML in first chronic phase, and 86% in those with MDS. Although patients with CML in first chronic phase (all age groups) experienced statistically significant increases in OS 1 year after alloHCT, patients with AML in CR1, ALL in second com-

plete remission (CR2), and MDS had relatively stable 1-year OS estimates of 75%, 70%, and 64%, respectively. For patients with AML, ALL, CML, or MDS who received a reduced-intensity or nonmyeloablative conditioning regimen during the period of 2004 to 2005, the OS estimates at day +100 and 1 year after alloHCT were 77% and 49%, respectively. For those with AML, ALL, CML, or MDS who received a myeloablative conditioning regimen and were age $\geq$ 60 years at time of HLA-matched sibling alloHCT (n = 74), OS estimates at day +100 and 1 year after alloHCT were 81% (95% CI, 71% to 89%) and 40% (95% CI, 28% to 52%) in 2004 to 2005 compared with 67% (95% CI, 54% to 79%) and 35% (95% CI 22% to 48%) in 1996 to 1997, respectively (*P* not significant for either comparison). OS estimates at day +100 and 1 year after alloHCT for 172 patients with AML, ALL, CML, or MDS age $\geq$ 60 years who received a reduced-intensity or nonmyeloablative conditioning regimen during the period of 2004 to 2005 were similar, at 83% (95% CI, 77% to 88%) and 44% (95% CI, 36% to 52%), respectively, and did not change over time.

OS After HLA-Matched Unrelated-Donor AlloHCT

Similar to sibling-donor HCTs, in every disease group that received a myeloablative conditioning regimen before unrelated-donor

Table 3. OS Estimates by Disease and Disease Status Subgroups, Stratified by Age at Time of HLA-Matched Sibling AlloHCT

Disease/Disease Status at HCT	1994 to 1995		1996 to 1997		1998 to 1999		2000 to 2001		2002 to 2003		2004 to 2005		P
	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	
AML in CR1 with myeloablative conditioning intensity													
All patients													
No. of patients	370		370		383		376		384		440		
100 days after HCT	85	81 to 88	87	84 to 90	90	86 to 93	88	84 to 91	92	89 to 94	94	91 to 96	<.001
1 year after HCT	69	65 to 74	70	66 to 75	72	67 to 76	67	62 to 72	74	69 to 78	75	71 to 80	.1662
Age 20-39 years at time of HCT*													
No. of patients	147		111		95		101		85		106		
100 days after HCT	86	80 to 91	92	86 to 96	89	82 to 95	89	82 to 94	92	85 to 97	100	84 to 93	.6187
1 year after HCT	72	64 to 79	73	65 to 81	74	64 to 82	73	64 to 81	76	66 to 85	78	69 to 86	.917
Age 40-59 years at time of HCT													
No. of patients	120		145		159		176		173		207		
100 days after HCT	77	70 to 84	79	72 to 85	89	84 to 94	85	80 to 90	91	86 to 95	89	84 to 93	.0065
1 year after HCT	59	50 to 68	63	55 to 71	69	61 to 76	59	51 to 66	71	64 to 78	69	62 to 76	.1051
AML in CR with myeloablative conditioning intensity													
All patients													
No. of patients	179		186		149		159		156		163		
100 days after HCT	77	70 to 83	82	76 to 87	88	82 to 93	85	79 to 90	85	79 to 90	92	87 to 96	.0018
1 year after HCT	62	55 to 69	63	56 to 70	69	61 to 77	59	51 to 67	64	56 to 71	70	62 to 77	.2937
Age 0-19 years at time of HCT													
No. of patients	128		146		104		108		106		109		
100 days after HCT	80	73 to 87	86	79 to 91	91	85 to 96	87	79 to 92	89	82 to 94	96	92 to 99	<.001
1 year after HCT	66	57 to 74	68	60 to 75	78	69 to 85	63	54 to 72	70	61 to 79	79	70 to 87	.0511
Age 20-39 years at time of HCT													
No. of patients	41		24		30		30		36		30		
100 days after HCT	66	51 to 79	NE		83	68 to 94	97	87 to 100	81	66 to 92	80	64 to 92	<.001†
1 year after HCT	48	33 to 64	NE		52	34 to 70	63	44 to 80	58	41 to 74	47	28 to 68	.7303†
CML in first chronic phase with myeloablative conditioning intensity													
All patients													
No. of patients	483		540		492		317		155		125		
100 days after HCT	84	81 to 87	88	85 to 90	89	87 to 92	91	87 to 94	99	96 to 100	98	94 to 100	<.001
1 year after HCT	71	66 to 75	72	68 to 76	80	76 to 83	82	77 to 86	89	83 to 93	92	86 to 96	<.001
Age 20-39 years at time of HCT													
No. of patients	225		226		164		127		76		52		
100 days after HCT	89	85 to 93	90	86 to 94	89	84 to 94	92	86 to 96	99	95 to 100	100	91 to 100	<.001
1 year after HCT	79	73 to 84	79	73 to 84	84	78 to 90	86	79 to 92	90	82 to 96	98	91 to 100	<.001
Age 40-59 years at time of HCT													
No. of patients	228		276		289		175		59		51		
100 days after HCT	78	72 to 83	86	81 to 89	89	86 to 93	91	86 to 95	98	93 to 100	98	92 to 100	<.001
1 year after HCT	61	55 to 68	67	61 to 73	77	72 to 82	78	71 to 84	83	72 to 92	84	70 to 94	<.001

(continued on following page)

(continued on following page)

Table 3. OS Estimates by Disease and Disease Status Subgroups, Stratified by Age at Time of HLA-Matched Sibling AlloHCT (continued)

Disease/Disease Status at HCT	1994 to 1995		1996 to 1997		1998 to 1999		2000 to 2001		2002 to 2003		2004 to 2005		P
	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	
MDS with myeloablative conditioning intensity													
All patients													
No. of patients	225		290		273		235		239		227		
100 days after HCT	71	65 to 77	75	70 to 80	76	71 to 81	82	77 to 87	85	80 to 89	88	84 to 92	< .001
1 year after HCT	54	48 to 61	51	45 to 57	57	51 to 63	58	51 to 65	61	55 to 68	64	58 to 71	.0488
Age 40-59 years at time of HCT													
No. of patients	121		157		173		153		166		148		
100 days after HCT	69	61 to 77	71	64 to 78	73	66 to 80	85	79 to 90	82	76 to 88	86	81 to 91	< .001
1 year after HCT	53	43 to 61	44	36 to 51	52	45 to 60	56	48 to 64	59	51 to 67	64	56 to 72	.0101
NHL with myeloablative conditioning intensity													
All patients													
No. of patients	234		456		467		345		342		272		
100 days after HCT	66	60 to 72	71	67 to 75	69	65 to 74	78	73 to 82	79	74 to 83	84	79 to 88	< .001
1 year after HCT	43	37 to 50	50	45 to 54	51	47 to 56	53	48 to 59	59	53 to 64	64	58 to 70	< .001
Age 20-39 years at time of HCT													
No. of patients	119		157		151		101		81		57		
100 days after HCT	69	60 to 77	81	74 to 87	72	65 to 79	81	72 to 88	75	65 to 84	82	72 to 91	.1169
1 year after HCT	51	42 to 60	55	47 to 63	51	43 to 60	56	46 to 66	57	46 to 68	64	50 to 77	.6346
Age 40-59 years at time of HCT													
No. of patients	102		272		288		215		223		190		
100 days after HCT	62	52 to 71	66	61 to 72	70	64 to 75	78	72 to 84	81	75 to 86	83	78 to 88	< .001
1 year after HCT	33	24 to 43	47	41 to 53	53	47 to 59	54	46 to 61	61	54 to 68	63	55 to 70	< .001
HL with any conditioning intensity													
All patients													
No. of patients	34		47		51		48		34		40		
100 days after HCT	62	45 to 77	64	50 to 77	84	72 to 93	62	48 to 75	82	67 to 93	79	66 to 91	.0299
1 year after HCT	32	18 to 49	41	28 to 56	61	46 to 75	53	38 to 67	62	45 to 78	57	41 to 73	.0498
AML, ALL, CML, or MDS with reduced/nonmyeloablative conditioning intensity													
All patients													
No. of patients	0		5		40		138		295		469		
100 days after HCT	NE		NE		64	48 to 78	66	58 to 74	79	74 to 83	77	73 to 81	.0148†
1 year after HCT	NE		NE		48	32 to 63	37	28 to 45	49	43 to 54	49	44 to 54	.0881†
NHL with reduced/nonmyeloablative conditioning intensity													
All patients													
No. of patients	0		10		49		152		218		203		
100 days after HCT	NE		NE		70	56 to 82	82	75 to 87	91	86 to 94	86	81 to 91	.0053
1 year after HCT	NE		NE		55	41 to 69	58	50 to 66	63	56 to 70	70	63 to 76	.1057

Abbreviations: ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CR1, first complete remission; CR2, second complete remission; HCT, hematopoietic cell transplantation; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; NE, not evaluable (sample size < 30 patients in this subgroup); NHL, non-Hodgkin lymphoma; OS, overall survival.

*Subgroup analyses by age are presented for highest-frequency groups.

†P values based on only those time cohorts with evaluable data (< six cohorts).

Table 4. OS Estimates by Disease and Disease Status Subgroups Stratified by Age at Time of HLA-Matched Unrelated-Donor AlloHCT

Disease/Disease Status at HCT													
AML in CR1 with myeloablative conditioning intensity													
All patients													
No. of patients	52		74		87		115		132		239		
100 days after HCT	63	50 to 76	65	54 to 75	70	60 to 79	77	69 to 84	80	73 to 86	86	81 to 90	< .001
1 year after HCT	48	35 to 62	36	25 to 47	48	38 to 59	52	42 to 61	55	46 to 63	63	56 to 69	.0026
Age 20-39 years at time of HCT*													
No. of patients	21		25		27		44		47		75		
100 days after HCT	NE		NE		NE		70	56 to 82	82	70 to 92	84	75 to 91	.2147†
1 year after HCT	NE		NE		NE		62	47 to 76	69	54 to 82	61	49 to 73	.6979†
Age 40-59 years at time of HCT													
No. of patients	9		22		32		43		63		122		
100 days after HCT	NE		NE		75	59 to 88	83	71 to 93	76	64 to 86	88	81 to 93	.1659†
1 year after HCT	NE		NE		56	39 to 73	39	24 to 54	46	33 to 58	61	51 to 71	.0551†
ALL in CR2 with myeloablative conditioning intensity													
All patients													
No. of patients	129		151		132		116		164		197		
100 days after HCT	66	58 to 74	70	62 to 77	71	62 to 78	75	67 to 82	78	71 to 84	91	87 to 95	< .001
1 year after HCT	43	34 to 51	45	37 to 53	49	40 to 58	40	31 to 50	54	46 to 62	67	60 to 74	< .001
Age 0-19 years at time of HCT													
No. of patients	107		110		85		76		109		122		
100 days after HCT	70	61 to 78	73	64 to 81	72	62 to 81	79	69 to 87	80	72 to 87	92	86 to 96	< .001
1 year after HCT	45	36 to 55	46	37 to 56	52	41 to 63	44	33 to 56	55	45 to 65	71	61 to 79	< .001
Age 20-39 years at time of HCT													
No. of patients	18		33		41		30		42		51		
100 days after HCT	NE		58	41 to 74	71	56 to 83	77	60 to 90	76	62 to 87	90	81 to 97	.0046†
1 year after HCT	NE		42	26 to 59	46	30 to 62	35	19 to 53	49	33 to 64	67	53 to 79	.0454†
CML in first chronic phase with myeloablative conditioning intensity													
All patients													
No. of patients	211		250		292		152		87		118		
100 days after HCT	71	65 to 77	70	64 to 75	74	69 to 79	75	68 to 81	80	71 to 88	87	81 to 93	< .001
1 year after HCT	51	44 to 57	54	48 to 61	59	53 to 64	60	52 to 68	65	54 to 75	71	62 to 80	.0057
Age 20-39 years at time of HCT													
No. of patients	100		122		129		76		50		46		
100 days after HCT	79	70 to 86	71	63 to 79	77	69 to 83	80	71 to 88	75	62 to 86	91	82 to 98	.0218
1 year after HCT	59	50 to 69	58	49 to 66	59	51 to 68	67	56 to 77	62	47 to 75	74	60 to 87	.3652
Age 40-59 years at time of HCT													
No. of patients	78		96		138		50		27		43		
100 days after HCT	62	51 to 72	69	59 to 78	70	62 to 77	72	59 to 83	NE		79	66 to 90	.3246†
1 year after HCT	36	26 to 47	48	38 to 58	57	49 to 65	52	38 to 66	NE		63	47 to 77	.0154†
MDS with myeloablative conditioning intensity													
All patients													
No. of patients	104		138		135		140		161		234		
100 days after HCT	64	54 to 73	62	54 to 70	59	51 to 67	67	59 to 75	74	67 to 81	78	72 to 83	< .001
(continued on following page)													

(continued on following page)

Table 4. OS Estimates by Disease and Disease Status Subgroups Stratified by Age at Time of HLA-Matched Unrelated-Donor AlloHCT (continued)

Disease/Disease Status at HCT	1994 to 1995		1996 to 1997		1998 to 1999		2000 to 2001		2002 to 2003		2004 to 2005		P
	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	
1 year after HCT	41	31 to 50	44	35 to 52	35	27 to 43	45	37 to 54	52	44 to 60	57	50 to 63	.001
Age 40-59 years at time of HCT													
No. of patients	33		59		54		73		87		132		
100 days after HCT	51	34 to 68	53	40 to 65	52	39 to 65	61	50 to 72	70	59 to 79	79	71 to 85	< .001
1 year after HCT	27	13 to 44	42	30 to 55	30	18 to 42	39	28 to 51	49	39 to 60	55	46 to 65	.0038
NHL with any conditioning intensity													
All patients													
No. of patients	23		73		94		167		222		222		
100 days after HCT	NE		49	37 to 60	55	45 to 65	63	55 to 70	67	61 to 73	81	75 to 85	< .001†
1 year after HCT	NE		40	29 to 52	32	22 to 42	37	30 to 45	48	41 to 55	54	46 to 61	< .001†
HL with any conditioning intensity													
All patients													
No. of patients	2		5		13		10		25		24		
100 days after HCT	NE		NE		NE		NE		84	67 to 95	88	72 to 97	.7255†
1 year after HCT	NE		NE		NE		NE		76	57 to 90	73	53 to 89	.8321†
AML, ALL, CML, or MDS with reduced/nonmyeloablative conditioning intensity‡													
All patients													
No. of patients	0		18		105		267		428		479		
100 days after HCT	NE		NE		77	68 to 85	84	79 to 88	84	81 to 88	87	83 to 89	.1581†
1 year after HCT	NE		NE		51	41 to 60	52	46 to 58	54	49 to 59	54	49 to 59	.88†

Abbreviations: ALL, acute lymphoblastic leukemia; alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CR1, first complete remission; CR2, second complete remission; HCT, hematopoietic cell transplantation; HL, Hodgkin lymphoma; MDS, myelodysplastic syndrome; NE, not evaluable (sample size < 30 patients in this subgroup); NHL, non-Hodgkin lymphoma; OS, overall survival.

‡Subgroup analyses by age are presented for highest-frequency groups.

†P value based on only those time cohorts with evaluable data (< six cohorts).

‡Insufficient number to evaluate each disease separately.

HCT, OS at 100 days after alloHCT demonstrated statistically significant increases over time (Table 4). In all patients, regardless of age, OS estimates at day +100 after alloHCT in the most recent cohort (2004 to 2005) ranged from 78% in those with MDS to 91% in those with ALL undergoing transplantation in CR2. Even in older patients age 40 to 59 years at time of alloHCT, OS estimates at day +100 after HCT were 87% for those with AML in CR1, 79% for those with CML in first chronic phase, and 79% in those with MDS. One-year OS estimates significantly increased over time, to 57% overall (55% in those age 40 to 59 years) in patients with MDS and 67% overall (71% in those age 0 to 19 years and 67% in those age 20 to 39 years) in patients with ALL in CR2 undergoing transplantation during the period of 2004 to 2005. OS estimates at 1 year after alloHCT for patients undergoing transplantation during the period of 2004 to 2005 ranged from 56% for those with AML in CR1 to 71% for those with CML in first chronic phase. For patients with AML, ALL, CML, or MDS who received a reduced-intensity or nonmyeloablative conditioning regimen in 2004 to 2005, OS estimates at day +100 and 1 year after alloHCT were 87% and 54%, respectively.

OS After UCB Transplantation With a Myeloablative Conditioning Regimen

OS estimates at day +100 after UCB transplantation significantly improved over time for patients with malignant disease (AML, ALL, CML, or MDS; Table 5); however, this improvement was limited to younger patients (age 0 to 19 years). OS estimates at day +100 and 1 year for older patients (age 20 to 39 years) treated for malignant diseases and for all patients treated for nonmalignant diseases showed

some improvement but did not significantly differ over time. The number of patients who underwent UCB transplantation using a reduced-intensity or nonmyeloablative conditioning regimen was too small for analysis of OS.

DISCUSSION

We identified some notable trends in the use of alloHCT in North America during the study time period. For instance, introduction of reduced-intensity and nonmyeloablative regimens has resulted in an increased use of alloHCT in older patients. The decrease in alloHCT for CML paralleled the introduction and increasing use of oral tyrosine kinase inhibitors for this disease. A greater proportion of patients with acute leukemia underwent alloHCT in CR in the more recent time period, indicating more timely transplantation among patients who were referred for alloHCT. Better understanding of the disease risk profile gained from leukemia clinical trials has likely contributed to early referral for alloHCT among patients who have a high probability of relapse with chemotherapy. Finally, the largest increase in alloHCT was attributed to the greater availability of unrelated donors, reflecting the efforts invested by the NMDP in enlarging and diversifying its donor registry.

In the past, alloHCT was associated with high TRM. However, our study, which represents approximately 70% to 90% of all alloHCTs performed in the United States, reinforces others demonstrating significantly improved survival rates over time.^{19,20} Although we were

Table 5. OS Estimates Stratified by Age at Time of Cord Blood HCT With Myeloablative Conditioning Intensity

	1994 to 1995		1996 to 1997		1998 to 1999		2000 to 2001		2002 to 2003		2004 to 2005		
Disease/Disease Status at HCT	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	OS (%)	95% CI	P
AML, ALL, CML, or MDS													
All patients													
No. of patients	65		140		219		332		375		375		
100 days after HCT	60	48 to 71	59	51 to 67	6356 to 69		65	60 to 70	78	74 to 82	78	74 to 82	< .001
1 year after HCT	49	37 to 61	44	36 to 52	4740 to 53		47	42 to 53	56	51 to 62	54	48 to 59	.0481
Age 0-19 years at time of HCT*													
No. of patients	63		122		145		260		315		283		
100 days after HCT	62	50 to 73	62	54 to 71	6961 to 76		69	63 to 74	82	77 to 86	83	78 to 87	< .001
1 year after HCT	51	38 to 63	47	38 to 56	5345 to 61		52	46 to 58	59	53 to 65	58	52 to 64	.2047
Age 20-39 years at time of HCT													
No. of patients	2		8		37		38		39		55		
100 days after HCT	NE		NE		65 49to79		63	47 to 78	61	45 to 76	69	56 to 80	.8766†
1 year after HCT	NE		NE		4327 to 60		33	19 to 49	41	25 to 57	45	30 to 61	.6954†
Nonmalignant disease													
All patients													
No. of patients	15		68		80		90		136		144		
100 days after HCT	NE		78	67 to 87	7464 to 83		84	76 to 91	84	77 to 89	85	79 to 91	.2884†
1 year after HCT	NE		64	52 to 75	6452 to 74		70	60 to 79	69	61 to 76	72	64 to 79	.6581†
Age 0-19 years at time of HCT													
No. of patients	13		65		80		89		135		141		
100 days after HCT	NE		77	66 to 86	7464 to 83		84	76 to 91	84	77 to 89	86	80 to 91	.2383†
1 year after HCT	NE		64	52 to 75	6452 to 74		71	61 to 80	69	61 to 77	72	64 to 79	.6285†

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndrome; NE, not evaluable (sample size < 30 patients in this subgroup); OS, overall survival.

*Subgroup analyses by age are presented for highest-frequency groups.

†P value based on only those time cohorts with evaluable data (< six cohorts).

unable to assess specific causes of death, our data demonstrate impressive reductions in all-cause mortality with traditional myeloablative conditioning regimens, especially at day 100 after transplantation. In addition, the increased use of reduced-intensity conditioning regimens allowed an older and more debilitated population to undergo alloHCT with similar survival outcomes, thus increasing the availability of alloHCT for more patients. We postulate that the significant improvements in OS over this time period have resulted from advancements in high-resolution HLA typing, improvements in supportive care after alloHCT, better patient selection, better understanding of patient and disease prognostic factors, and earlier referral for transplantation.

Use of alloHCT for the treatment of CML has decreased, presumably because of US Food and Drug Administration approval of tyrosine kinase inhibitors in 2001. It is too early to determine the ramifications of using alloHCT as salvage treatment for CML that is more advanced and/or heavily pretreated on long-term survival or complications after alloHCT. As use of tyrosine kinase inhibitors increases, alloHCT may still play a role in the management of patients with CML and Philadelphia chromosome-positive ALL.

AlloHCT remains an important therapy to cure a variety of hematologic disorders. Although significant improvements in early (day +100) OS have been achieved, additional improvements in later (1 year) OS are still needed. Additional advancements to reduce the burden of GVHD and disease relapse after alloHCT are priority research areas.

REFERENCES

1. Pasquini MC, Wang Z: Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides, 2010. <http://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/pages/index.aspx>
2. Pulsipher MA, Boucher KM, Wall D, et al: Reduced-intensity allogeneic transplantation in pediatric patients ineligible for myeloablative therapy: Results of the Pediatric Blood and Marrow Transplant Consortium Study ONC0313. *Blood* 114:1429-1436, 2009
3. Laport GG, Sandmaier BM, Storer BE, et al: Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. *Biol Blood Marrow Transplant* 14:246-255, 2008
4. Servais S, Baron F, Beguin Y: Allogeneic hematopoietic stem cell transplantation (HSCT) after reduced intensity conditioning. *Transfus Apher Sci* 44:205-210, 2011
5. Shimoni A, Hardan I, Shem-Tov N, et al: Allogeneic hematopoietic stem-cell transplantation in AML and MDS using myeloablative versus reduced-intensity conditioning: The role of dose intensity. *Leukemia* 20:322-328, 2006
6. Estey E, de Lima M, Tibes R, et al: Prospective feasibility analysis of reduced-intensity conditioning (RIC) regimens for hematopoietic stem cell transplantation (HSCT) in elderly patients with acute myeloid leukemia (AML) and high-risk myelodysplastic syndrome (MDS). *Blood* 109:1395-1400, 2007
7. Yanik G, Levine JE, Ratanatharathorn V, et al: Tacrolimus (FK506) and methotrexate as prophylaxis for acute graft-versus-host disease in pediatric allogeneic stem cell transplantation. *Bone Marrow Transplant* 26:161-167, 2000
8. Kasper C, Sayer HG, Mügge LO, et al: Combined standard graft-versus-host disease (GVHD) prophylaxis with mycophenolate mofetil (MMF) in allogeneic peripheral blood stem cell transplantation from unrelated donors. *Bone Marrow Transplant* 33:65-69, 2004
9. Spellman S, Setterholm M, Maiers M, et al: Advances in the selection of HLA-compatible donors: Refinements in HLA typing and matching over the first 20 years of the National Marrow Donor Program Registry. *Biol Blood Marrow Transplant* 14:37-44, 2008 (suppl 9)
10. Johansen KA, Schneider JF, McCaffree MA, et al: Efforts of the United States' National Marrow Donor Program and Registry to improve utilization and representation of minority donors. *Transfus Med* 18:250-259, 2008
11. Barker JN, Byam CE, Kernan NA, et al: Availability of cord blood extends allogeneic hematopoietic stem cell transplant access to racial and ethnic minorities. *Biol Blood Marrow Transplant* 16:1541-1548, 2010
12. Giralot SA, Arora M, Goldman JM, et al: Impact of imatinib therapy on the use of allogeneic haematopoietic progenitor cell transplantation for the treatment of chronic myeloid leukaemia. *Br J Haematol* 137:461-467, 2007
13. Centers for Medicare and Medicaid Services: National Coverage Determination (NCD) for Stem Cell Transplantation (110.8.1), Version 5. <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=45&ncdver=5&bc=BAAAgAAAAA&>
14. CareFirst BlueCross BlueShield: Medical Policy 7.03.003: High-dose chemotherapy/radiation therapy with allogeneic stem-cell support. <http://notesnet.carefirst.com/e-commerce/medicalpolicy.nsf/wwwwebtablex/49a275cf5e4e59988525770a004b8fdb?OpenDocument>
15. Cigna: Medical coverage policy: Stem-cell transplantation for myelodysplastic syndromes. http://www.cigna.com/customer_care/health_care_professional/coverage_positions/medical/mm_0187_coveragepositioncriteria_stem_cell_transpl_myelodysplastic_syndr.pdf
16. Cigna: Medical coverage policy: Stem-cell transplantation for multiple myeloma and POEMS. http://www.cigna.com/customer_care/health_care_professional/coverage_positions/medical/mm_0294_coveragepositioncriteria_stem_cell_transpl_mult_myeloma_poems.pdf
17. National Cancer Institute: Surveillance, Epidemiology, and End Results. <http://seer.cancer.gov/>
18. US Department of Commerce: US Census Bureau. <http://www.census.gov/main/www/access.html>
19. Gooley TA, Chien JW, Pergam SA, et al: Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med* 363:2091-2101, 2010
20. Remberger M, Ackefors M, Berglund S, et al: Improved survival after allogeneic hematopoietic stem cell transplantation in recent years: A single-center study. *Biol Blood Marrow Transplant* 17:1688-1697, 2011

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Steven Joffe, Genzyme/sanofi-aventis (C) **Stock Ownership:** None **Honoraria:** Christopher Bredeson, sanofi-aventis **Research Funding:** Christopher Bredeson, Otsuka **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Provision of study materials or patients: Navneet S. Majhail

Collection and assembly of data: Theresa Hahn, Philip L. McCarthy,

Anna Hassebroek, Navneet S. Majhail

Data analysis and interpretation: All authors

Manuscript writing: Theresa Hahn, Philip L. McCarthy, Navneet S. Majhail

Final approval of manuscript: All authors

Affiliations

Theresa Hahn and Philip L. McCarthy Jr, Roswell Park Cancer Institute, Buffalo; Luis M. Isola, Mount Sinai Medical Center, New York, NY; Anna Hassebroek, Center for International Blood and Marrow Transplant Research; Navneet S. Majhail, National Marrow Donor Program, Minneapolis, MN; Christopher Bredeson, Ottawa Hospital Blood and Marrow Transplant Program, Ottawa, Ontario, Canada; James L. Gajewski and Richard T. Maziarz, Oregon Health and Science University, Portland, OR; Gregory A. Hale, All Children's Hospital, St Petersburg, FL; Hillard M. Lazarus, University Hospitals Case Medical Center, Cleveland, OH; Stephanie J. Lee, Fred Hutchinson Cancer Research Center, Seattle, WA; Charles F. LeMaistre, Sarah Cannon Research Institute, Nashville, TN; Fausto Loberiza, University of Nebraska Medical Center, Omaha, NE; J. Douglas Rizzo, Center for International Blood and Marrow Transplant Research, Milwaukee, WI; Steven Joffe, Dana-Farber Cancer Institute and Children's Hospital; and Susan Parsons, Tufts Medical Center, Boston, MA.

Support

The Center for International Blood and Marrow Transplant Research is supported by Public Health Service Grant/Cooperative Agreement No. U24-CA76518 from the National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), and National Institute of Allergy and Infectious Diseases; by Grant/Cooperative Agreement No. 5U01HL069294 from NHLBI and NCI; by Contract No. HHSH234200637015C with the Health Resources and Services Administration; by Grants No. N00014-06-1-0704 and N00014-08-1-0058 from the Office of Naval Research; and by grants from Allos, Amgen, Angioblast, Ariad, Be the Match Foundation, BlueCross BlueShield Association, Buchanan Family Foundation, CaridianBCT, Celgene, CellGenix, Children's Leukemia Research Association, Fresenius-Biotech North America, Gamida Cell Teva Joint Venture, Genentech, Genzyme, GlaxoSmithKline, HistoGenetics, Kiadis Pharma, Leukemia and Lymphoma Society, Medical College of Wisconsin, Merck, Millennium Pharmaceuticals, Takeda Oncology, Milliman USA, Miltenyi Biotec, National Marrow Donor Program, Optum Healthcare Solutions, Osiris Therapeutics, Otsuka America Pharmaceutical, RemedyMD, sanofi-aventis, Seattle Genetics, Sigma-Tau Pharmaceuticals, Soligenix, StemCyte, Stemsoft Software, Swedish Orphan Biovitrum, Tarix Pharmaceuticals, Teva Neuroscience, THERAKOS, and Wellpoint; and by an anonymous donation to the Medical College of Wisconsin.