

Individual Physician Practice Variation in Hematopoietic Cell Transplantation

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ABSTRACT

Purpose

Previous studies have evaluated practice variation in hematopoietic cell transplantation (HCT) among transplant centers and countries. There are no studies investigating individual physician practice variation in HCT.

Methods

An international Internet-based survey of transplant physicians collected data on medical decisions made by adult and pediatric HCT physicians. Multivariable analyses identified practitioner and transplant center characteristics predictive of medical decision making.

Results

Analysis of 526 assessable respondents showed a wide variation in management approaches to specific clinical scenarios. Pediatric and adult transplant physicians differed significantly in their management strategies for chronic myeloid leukemia, acute and chronic graft-versus-host disease, and choice of graft source for patients with aplastic anemia. Among adult transplant physicians, there was little agreement on the patient factors favoring reduced intensity conditioning or myeloablative conditioning.

Conclusion

These results emphasize the heterogeneity of worldwide transplant practices. Local preferences or biases likely result in similar patients being offered different transplant and treatment procedures. The degree of practice variation also highlights the need for clinical trials to clarify areas of controversy. Where clinical trials are not feasible, data from observational studies may be the best available evidence to guide practice.

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INTRODUCTION

Ideally, patients with similar diseases and clinical situations would obtain the same treatment recommendations and care regardless of the physician they see. If they do not, then “practice variation” exists. Practice variation may be due to controversy over the effectiveness of various procedures¹ or differences in physician practice style.² Undesirable practice variation may result from lack of familiarity with or adherence to evidence-based practice, external nonmedical influences on physicians (eg, practice environment, reimbursement structure),³ or consideration of patient characteristics (eg, race, ethnicity, sex, age, personal resources) if these features should not influence treatment recommendations.

Previous studies evaluating practice variation in hematopoietic cell transplantation (HCT) show that transplant activity varies by country⁴ and is associated with gross national income.⁵⁻⁷

Other studies show that transplant centers vary in their prophylaxis strategies and management of transplant complications.⁸⁻¹³ However, no HCT studies have measured individual physician decision making or explored physician and transplant center characteristics that may be associated with those decisions.

Understanding practice variation offers different benefits depending on the strength of the evidence supporting a clinical practice. If evidence is scant, then wide practice variation can identify areas of controversy worthy of study and increase tolerance for practices different from one's own. Potential areas for cost saving can be identified, because in the absence of improved patient outcomes, the least costly approach is justifiable.¹⁴ If evidence for a practice is strong, then documentation of practice variation highlights areas where better education, dissemination of information, and quality improvement systems can improve care.^{15,16}

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In all cases, appreciation of practice variation can help with planning and interpreting clinical trials.

Physician surveys are ideal tools for studying practice variation in a cost efficient and highly controlled manner, because many physicians can be presented with the identical clinical scenario and treatment options.¹⁷⁻²⁰ We conducted an Internet-based survey of transplant physicians to examine practice variation in HCT. Our intent was to document the degree of practice variation attributable to nonpatient factors.

METHODS

Survey Development

A draft survey was prepared by the authors and subsequently modified after pilot testing. The sociodemographic questions were taken from similar studies previously conducted by the authors.¹² Individual items were constructed to measure practice variation in medical decision making. The self-administered survey contained 44 to 50 items depending on whether respondents identified themselves as adult or pediatric transplant physicians. The survey took 10 to 20 minutes to complete, and respondents were allowed to skip questions. A copy of the survey may be obtained by contacting the corresponding author.

Eight questions presented clinical scenarios and elicited treatment recommendations. Two of the eight clinical scenarios and two questions related to acute and chronic graft-versus-host disease (GVHD) were identical between pediatric and adult versions. Adult transplant physicians were also asked six questions about choice of myeloablative versus reduced intensity conditioning (RIC) in specified situations. Eleven additional questions collected physician and transplant center characteristics. This report focuses on decision making related to indications for transplantation, choice of stem-cell source, and treatment of acute and chronic GVHD in adult and pediatric practice; other data will be reported elsewhere.

Data Collection

The Dana-Farber Cancer Institute's institutional review board approved the study and waived the requirement for documentation of informed consent. A description of the survey and invitation to participate were emailed to people with the title "Dr" in the Center for International Blood and Marrow Transplant Research (CIBMTR) database. In appreciation, participation in a drawing for two cash prizes was offered to survey respondents. Each invitation included a unique link to allow survey completion or opting out. Three e-mail reminders were subsequently sent at weekly intervals. The first drawing occurred 1 week after the first e-mail reminder and the second drawing took place a week after the third e-mail reminder. Surveying occurred between November 18, 2005, and December 15, 2005. Respondents completed the survey online. Many e-mail invitations may not have reached their intended recipients. In February 2007, the CIBMTR attempted to confirm e-mail addresses of its members. Approximately 40% of physician e-mail addresses were no longer active (M. Eapen, personal communication, April 2007).

Two thousand two hundred twenty-nine emails were sent to potentially eligible subjects. Five hundred seventy were not eligible to respond due to confirmation of undeliverable e-mail, duplicate addresses, or confirmation that the recipient was ineligible (for example, not a transplantation physician, retired). Five hundred forty responses were received of which 526 were assessable. Surveys (n = 14) were excluded if respondents answered fewer than one half of the medical decision making or supportive care questions. Only 84 recipients actively declined to participate in the study; 1,035 did not respond in any way to the three emails, and we are unable to further classify this group into passive nonrespondents versus inactive e-mail addresses. Thus, the assessable response rate was somewhere between 32% of all potentially eligible invitations (526 of 1,659) and 84% of confirmed invitations (526 of 624). Two hundred forty-eight responded to

the first e-mail (47%), with subsequent emails garnering 147 (28%), 75 (14%), and 56 (11%) of assessable respondents.

Biostatistical Analysis

Descriptive statistics are reported for sociodemographics and practice characteristics. Comparisons between adult and pediatric respondents are based on χ^2 , Fisher's exact, Mantel-Haenszel χ^2 , or Wilcoxon rank sum tests as appropriate. Regions of the world were classified according to the United Nations World Macro Regions classification system.²¹ Multivariate forward stepwise logistic modeling was used to determine if physician or transplant center characteristics were associated with medical decision making in several scenarios. These scenarios were selected a priori based on the level of controversy and/or the availability of data to guide decisions. Potential predictors included United States versus non-United States, physician sex, age, time in practice, and amount of clinical and research time, whether the practice setting was community, academic or both, center size, whether the focus was on adults or pediatric patients, and whether the respondent primarily performed autologous or allogeneic procedures. Adult transplant physicians were presented with six scenarios and asked to recommend RIC or myeloablative conditioning. A summary variable from 0 to 6 was used to indicate strength of recommendation for RIC conditioning and linear regression used to identify predictors among allogeneic transplant physicians. In addition, for the RIC analysis, respondents' self-classification as primarily involved in RIC or myeloablative procedures was included as a potential predictor.

Individual respondents were considered unassessable for particular questions if either they did not answer the question, indicated they did not see those types of patients, or otherwise indicated the question did not pertain to them. Respondents providing write in answers to the "other, specify" option were recategorized into existing response options if appropriate.

Within the tables, results are presented if more than 5% of either pediatric or adult transplant physicians endorsed an option.

To assess nonresponder bias, physician characteristics and responses to the vignettes were compared between three groups: those responding to the initial e-mail, those responding to the first reminder e-mail, and those responding to either the second or third reminder emails. There were no differences in the distribution of characteristics and responses.

RESULTS

Physician Practice Characteristics

Physician and center descriptions are presented in Table 1. Of note, the sample was predominantly male (74%), practiced in an academic center (73%), and was clinically active. The median age was 47 years, and 57% practiced in the United States. Half had completed fellowship before 1991. Three hundred eighty-three (73%) considered themselves adult transplant physicians while 142 (27%) considered themselves pediatric transplant physicians. Adult and pediatric transplant physicians were of similar age and time since training. They reported equal frequencies of being in academic versus community practices and a similar distribution of time spent in administration and teaching, basic, and clinical research. However, pediatricians were more likely to be women (38% v 19%; $P < .0001$) and to practice in the United States (70% v 54%; $P = .0015$). Pediatricians spent less time in clinical care ($P = .01$), had less clinic ($P < .0001$) and ward time ($P = .01$), and reported smaller transplant practices ($P < .0001$) with a greater percentage of myeloablative allogeneic procedures.

Medical Decision Making

Tables 2,3,4, and 5 summarize answers to the scenarios posed to adult and pediatric transplant physicians. Specifically, Table 2 compares adult and pediatric physicians' responses to identical vignettes

Table 1. Physician and Center Characteristics

Characteristic	All Respondents		Adult		Pediatric		P
	No.	%	No.	%	No.	%	
No. of respondents	526	384	73	142	27	—	
Primary procedure type							< .0001
Autologous	165	31	152	40	13	9	
Myeloablative allogeneic	302	57	178	46	124	87	
Reduced intensity conditioning	59	11	54	14	5	4	
Median age, years	47		48		46		
Range*	31-72		31-72		32-68		.14
Sex							< .0001
Male	390	74	303	79	87	61	
Female	125	24	71	18	54	38	
Missing	11	2	10	3	1	1	
Year completed training							.10
Before 1980	58	11	46	12	12	8	
1980-1989	158	30	118	31	40	28	
1990-1999	216	41	157	41	59	42	
2000 or later	80	15	53	14	27	19	
Missing	14	3	10	3	4	3	
Practice setting							.34
Academic center	382	73	274	71	108	76	
Community setting	49	9	40	10	9	6	
Both academic and community	86	16	63	16	23	16	
Missing	9	2	7	2	2	1	
Percentage of time, median*							
Patient care		60		60		50	.01
Administration/teaching		20		20		20	.13
Basic research		0		0		0	.47
Clinical research		20		20		20	.79
Attending responsibilities, median*							
Days in clinic	2.5		3		2		< .0001
Months on an inpatient service	4		4		4		.01
Total annual HCT procedures at center, median*	70		80		40		
Range	2-1,000		7-1,000		2-450		< .0001
Procedures at center, median*							
Autologous		40		50		30	< .0001
Myeloablative allogeneic		40		30		60	< .0001
Reduced intensity conditioning		15		20		5	< .0001
Country							.0008
United States	301	57	203	53	98	69	
Other	213	40	172	45	41	29	
Missing	12	2	9	2	3	2	
Region							.02
North America	330	63	225	59	105	74	
Latin America	37	7	32	8	5	4	
Europe	87	17	72	19	15	11	
Asia	36	7	28	7	8	6	
Africa	3	1	3	1	0	0	
Australia/New Zealand	21	4	15	4	6	4	
Missing	12	2	9	2	3	2	

NOTE. Percentages are based on available data.
Abbreviation: HCT, hematopoietic cell transplantation.
*Seven to 17 respondents did not answer each question.

(except in one case where the patient's age differed by 5 years). Pediatricians were more likely than adult transplant physicians to recommend allogeneic transplantation to an 18-year-old with chronic phase chronic myeloid leukemia (CML) and an HLA-matched sibling (70% v 35%; $P < .0001$). Pediatricians were somewhat more likely than adult transplant physicians to recommend an alternative chem-

otherapy regimen for a 20-year-old with resistant blast crisis CML (50% v 38%); adult transplant physicians, in contrast, were more likely to endorse allogeneic HCT while in blast crisis or best supportive care. Pediatricians favored bone marrow over peripheral blood as a stem-cell source for young patients undergoing matched sibling transplantation for aplastic anemia compared with adult transplant physicians

Practice Variation in HCT

Table 2. Comparison of Adult and Pediatric Practice

Scenario	Adult		Pediatric		P	
	No.	%	No.	%		
An 18-year-old otherwise healthy young man has just been diagnosed with CML and has an HLA-identical sibling; what would you recommend?						
Proceeding to allogeneic HCT (regardless of response to imatinib)	132	34.9	96	69.6	< .0001	
A trial of imatinib with allogeneic HCT reserved if an inadequate response	246	65.1	42	30.4		
Not assessable	6		4			
A 20-year-old otherwise healthy woman has CML in myeloid blast crisis that developed while taking imatinib; she is not a candidate for any of the new targeted CML drugs and has not gone into remission after a cycle of AML-type chemotherapy; she has a molecularly matched unrelated donor available; what would you recommend?					.02	
Allogeneic HCT using the unrelated donor while in blast crisis	184	49.5	54	43.6		
Alternative chemotherapy regimen	140	37.6	62	50.0		
Best supportive care (including hydroxyurea, symptom management)	48	12.9	8	6.5		
Not assessable	12		18			
A 20-year-old* otherwise healthy man with newly diagnosed idiopathic severe aplastic anemia is preparing to proceed to transplantation; his HLA-matched sibling donor is an 18-year-old and willing to donate bone marrow or peripheral blood; what would you recommend?						
Bone marrow	253	68.0	122	89.7	< .0001	
Peripheral blood	119	32.0	14	10.3		
Not assessable	12		6			
Therapy for steroid-refractory acute GVHD						
Mycophenolate mofetil (Cellcept)	71	20.2	17	12.6	< .0001	
Horse antithymocyte globulin (ATGAM)	48	13.7	19	14.1		
Rabbit antithymocyte globulin (Thymoglobulin)	63	18.0	4	3.0		
Denileukin diftitox (Ontak)	19	5.4	2	1.5		
Daclizumab (Zenapax)	29	8.3	18	13.3		
Etanercept (Enbrel)	5	1.4	8	5.9		
Infliximab (Remicade)	28	8.0	28	20.7		
Pentostatin (Nipent)	18	5.1	4	3.0		
Higher dose methylprednisolone (greater than 2 mg/kg/d)	26	7.4	20	14.8		
Other (sirolimus, extracorporeal photopheresis, alemtuzumab)	44	12.5	15	11.1		
Not assessable	33		7			
Therapy for steroid-refractory chronic GVHD (n = 517)						
Mycophenolate mofetil (Cellcept)	190	52.1	68	49.6	.0002	
Sirolimus (Rapamycin)	24	6.6	5	3.7		
Extracorporeal photopheresis	35	9.6	6	4.4		
Pentostatin (Nipent)	6	1.6	9	6.6		
Higher dose methylprednisolone (> 2 mg/kg/d)	22	6.0	22	16.1		
Calcineurin inhibitor: write in answer	44	12.1	10	7.3		
Other (anti-thymocyte globulin, denileukin diftitox, daclizumab, alemtuzumab, etanercept, infliximab, rituximab, hydroxychloroquine, azathioprine, thalidomide, acitretin, clofazimine)	44	12.1	17	12.4		
Not assessable	19		5			
A patient is diagnosed with chronic GVHD of the liver and skin; she is given 1 mg/kg steroids and promptly responds with normalization of liver function tests and resolution of her rash when you next see her 2 weeks later; how would you manage her immunosuppression?						
Begin to decrease her steroid dose	239	65.0	66	47.5		< .0001
Continue steroids at 1 mg/kg for at least 4 more weeks before attempting a taper	120	32.6	63	45.3		
Continue steroids at 1 mg/kg for at least 3 more months before attempting a taper	9	2.5	10	7.2		
Not assessable	16		3			
When tapering steroids in a patient with chronic GVHD, do you aim for every other day dosing at some point in the taper?						
No, I taper the daily dose until it is discontinued	80	21.8	18	13.0	.02	
Yes, one of my goals is to taper to alternate day dosing	287	78.2	121	87.1		
Not assessable	17		3			

Abbreviations: CML, chronic myeloid leukemia; HCT, hematopoietic cell transplantation; AML, acute myeloid leukemia; GVHD, graft-versus-host disease. *Fifteen-year-old for the pediatric scenario.

Table 3. Adult Medical Decision Making

Scenario	No.	%
A 30-year-old otherwise healthy man with multiple myeloma has achieved a minimal disease state with conventional chemotherapy; he has an HLA-identical sibling; what would you recommend?		
Single autologous transplant	97	25.9
Double (tandem) autologous transplant	56	15.0
Autologous transplant followed by a reduced intensity conditioning allogeneic transplant	155	41.4
Allogeneic transplant (myeloablative or reduced intensity conditioning)	66	17.7
A 41-year-old otherwise healthy woman with stage IV diffuse large B-cell lymphoma initially involving bone marrow achieved a 6-month remission with CHOP-rituxan; she then relapsed and has achieved a very good partial remission to salvage chemotherapy; she has an HLA-matched identical sibling; what would you recommend?		
Autologous peripheral-blood stem-cell transplant, with or without further chemotherapy first	249	65.5
Myeloablative allogeneic stem-cell transplant	87	22.9
Reduced intensity conditioning allogeneic transplant	44	11.6
A 40-year-old otherwise healthy man has AML with normal cytogenetics in second complete remission after reinduction; he currently has normal blood counts and an HLA-matched sibling; what would you recommend?		
Cycle of consolidation therapy, followed by allogeneic HCT	73	19.2
Allogeneic HCT, without consolidation	298	78.4
Autologous HCT, with or without further consolidation	7	1.8
Consolidation therapy without HCT	2	0.5
A 30-year-old otherwise healthy man with AML and t(8;21) receives chemotherapy and stays in remission for 15 months; he then comes to clinic and is found to have relapsed (20% blasts in marrow although none in peripheral blood); a matched unrelated volunteer donor is readily available (allele-matched at HLA-A,-B,-C, DRB1); what would you recommend?		
Unrelated donor transplant in first relapse	82	21.8
Autologous transplant after attempting to achieve a second complete remission	26	6.9
Unrelated donor transplant after attempting to achieve a second complete remission	262	69.5
Reinduction chemotherapy without transplantation	7	1.9
A 25-year-old otherwise healthy woman has acute lymphoblastic leukemia in relapse after achieving initial remission with multiagent chemotherapy that lasted 3 years; she continues to have 5% circulating blasts despite one attempt at reinduction; she has an HLA-matched sibling donor available; what would you recommend?		
Allogeneic HCT in first relapse using the related donor	198	53.2
Second attempt at reinduction, with or without subsequent transplantation	172	46.2
Best supportive care (including hydroxyurea, symptom management)	2	0.5

NOTE. For each question, four to 12 respondents would not provide a recommendation or do not see this type of patient.

Abbreviations: CHOP, cyclophosphamide, adriamycin, vincristine, and prednisone; AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation.

(90% v 68%; $P < .0001$). The fact that 32% of adult transplant physicians recommended peripheral blood over bone marrow for young patients with aplastic anemia is surprising given reports suggesting good outcomes with bone marrow and higher chronic GVHD and mortality with peripheral blood.^{22,23} When choosing therapy for steroid-refractory acute GVHD where there is no established standard of care, there was little agreement in either group, with no agent garnering more than 21% of the vote. Pediatricians favored infliximab (21%), higher dose steroids (15%), horse antithymocyte globulin (ATG; 14%), daclizumab (13%), and mycophenolate mofetil (MMF; 13%) compared with adult physicians who favored MMF (20%), rabbit ATG (18%), and horse ATG (14%). Although approximately half of both adult and pediatric transplant physicians selected MMF as the next agent for steroid-refractory chronic GVHD, pediatricians also endorsed higher dose steroids (16%), calcineurin inhibitors (7%), and pentostatin (7%) while adult transplant physicians favored calcineurin inhibitors (12%), extracorporeal photopheresis (10%), and sirolimus (7%) instead. When tapering steroids after successful control of chronic GVHD, pediatricians waited longer before initiating a taper.

Table 3 summarizes the results of scenarios posed only to adult transplant physicians. The lack of clear consensus for most of the situations is notable. The role of autologous and allogeneic hematopoietic transplantation in multiple myeloma, is particularly contro-

versial. Forty-one percent of physicians endorsed autologous transplantation followed by RIC allogeneic transplantation for a patient with chemotherapy-sensitive myeloma even though this is the focus of an ongoing Clinical Trials Network study and a recent high profile publication.²⁴ When all options offered dismal outcomes (a 25-year-old with relapsed acute lymphoblastic leukemia and persistent disease after one attempt at reinduction), physicians were evenly divided over proceeding directly to transplantation (53%) or attempting another induction regimen (46%).

Table 4 summarizes responses to the pediatric scenarios. As observed among adult transplant physicians, pediatric transplant physicians also differed in their responses to the clinical scenarios presented. Approximately 50% of physicians recommended a matched related donor transplant for a patient with low-risk AML although several published reports indicate comparable outcomes with the intensified chemotherapy regimens used in the current era.^{25,26} When faced with a patient with high-risk AML, continuing chemotherapy was preferred by one fourth of respondents over an allele-matched unrelated donor transplant although several reports support the later treatment when a well-matched unrelated donor is available.^{27,28}

Table 5 presents data regarding choice of myeloablative or RIC for specific scenarios where an HLA-matched sibling is available. For

Table 4. Pediatric Medical Decision Making

Scenario	No.		%	
A 7-year-old otherwise healthy girl with B-precursor ALL was treated on the current standard risk ALL protocol; she develops an isolated CNS relapse 5 months after completion of therapy; she has an HLA-matched sibling; what would you recommend?				
CNS-directed and continuation therapy	68		48.9	
HLA-identical sibling transplant	71		51.1	
A 6-year-old girl with standard-risk ALL has experienced a bone marrow relapse during her second year of chemotherapy; she is now in remission after one reinduction cycle; she is an only child, but does have both a molecularly matched unrelated donor and a 1 antigen mismatched unrelated cord blood unit (with adequate cellularity) available; what would you recommend?				
Transplant using the matched unrelated donor	104		75.9	
Transplant using the 1 antigen mismatched cord blood unit	33		24.1	
A 6-month-old male infant, diagnosed with ALL, t (4;11) has marrow and CNS involvement at diagnosis; he achieves a morphologic and cytogenetic first complete remission; he is an only child, but there is a cord blood unit with adequate cellularity, mismatched at one HLA-A locus; what would you recommend?				
Recommend cord blood transplant	97		68.8	
Do not recommend cord blood transplant	44		31.2	
A 14-year-old boy presents with AML; cytogenetics reveal monosomy 7; he is now in remission after induction chemotherapy; he does not have any sibling donors but does have an available molecularly matched unrelated donor; which of the following treatment strategies would you recommend?				
Transplant in first complete remission using the unrelated donor	106		75.2	
Completion of chemotherapy for AML	35		24.8	
An 11-year-old girl presents with AML; cytogenetics reveal t(8;21); she is in remission after induction chemotherapy; her 14-year-old sister is a 6/6 HLA match; what would you recommend?				
Transplant in first complete remission using the sibling donor	69		49.3	
Completion of chemotherapy for AML	71		50.7	

NOTE. For each question, one to five respondents would not provide a recommendation or do not see this type of patient. Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

five of six questions regarding RIC, respondents who identified themselves primarily as RIC transplant physicians ($n = 54$) were more likely to recommend RIC than myeloablative transplant physicians ($n = 175$). Review of the responses to the six scenarios suggests that disease type is the primary determinant of conditioning regimen choice, although older age and poor performance status also appear to favor RIC. RIC allogeneic transplantation is a rapidly developing area in which the indications are not well established and multiple different regimens are under study.

Table 6 presents the physician and transplant center characteristics predictive of selected medical decisions. Several physician and practice factors were associated with medical decision making. However, in multivariate models accounting for these other factors, pediatricians were still more likely to recommend HLA-matched sibling

transplantation instead of continued imatinib for an 18-year-old with chronic phase CML, and bone marrow instead of peripheral blood for a patient with aplastic anemia. Among pediatricians, transplant physicians in the United States were more likely to recommend HLA-matched sibling transplantation instead of chemotherapy for an 11-year-old girl with t(8;21) in first complete remission.

DISCUSSION

We found considerable variation in medical decision making among adult and pediatric HCT physicians participating in the CIBMTR. Our results suggest that similar patients are receiving different treatment recommendations across physicians and centers, likely reflecting a

Table 5. Adult Myeloablative Versus Reduced Intensity Conditioning

Scenario	Myeloablative		Reduced Intensity	
	No.	%	No.	%
A 57-year-old man with AML in second complete remission	121	34.0	235	66.0
A 45-year-old woman with low-grade lymphoma in responsive second relapse	89	25.1	265	74.9
A 34-year-old woman with AML in third complete remission, no comorbidities, and a Karnofsky performance status of 60%	114	32.9	233	67.2
A 45-year-old man with CML in chronic phase progressing on imatinib	283	79.3	74	20.7
A 34-year-old woman with MDS developing 4 years after an autologous transplant for NHL	227	63.8	129	36.2
A 49-year-old man with hypertension, insulin-dependent diabetes, and Philadelphia chromosome positive ALL in first complete remission	255	72.0	99	28.0

NOTE. For each question, two to 12 respondents do not see this type of patient. Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma; ALL, acute lymphoblastic leukemia.

Table 6. Predictors of Medical Decisions

Recommendation	Predictor	OR	95% CI	SE	P
HLA-matched sibling transplant instead of continued imatinib therapy for an 18-year-old with chronic phase CML	Pediatrician v adult	3.5	2.3 to 5.4		< .0001
	Allogeneic v autologous	1.9	1.3 to 3.0		.002
Bone marrow instead of peripheral blood for a patient with aplastic anemia	Pediatrician v adult	4.4	2.2 to 8.6		< .0001
	Allogeneic v autologous	2.7	1.7 to 4.3		< .0001
	Larger v smaller center	2.3	1.4 to 3.7		.0005
	Non-US v US center	2.0	1.2 to 3.2		.004
Pediatricians only: HLA-matched sibling transplant instead of CNS-direct and continuation therapy for a 7-year-old girl with ALL and isolated CNS relapse	More v less clinical time	3.4	1.6 to 7.1		.001
Pediatricians only: HLA-matched sibling transplant instead of completion of chemotherapy for an 11-year-old girl with t(8;21) AML in first complete response	US v non-US	7.6	3.1 to 19.0		< .0001
Adult transplant physicians only: RIC instead of myeloablative conditioning	RIC v myeloablative	1.4*		0.2	< .0001
	Community v academic	1.1*		0.4	.003
	Male v female	0.6*		0.2	.004
	Non-US v US	0.4*		0.2	.008

Abbreviations: OR, odds ratio; CML, chronic myeloid leukemia; US, United States; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; RIC, reduced intensity conditioning.

*Parameter estimate from linear regression.

paucity of robust clinical trials on which to base uniform clinical decision making. One area of striking variation is the differential recommendations of adult and pediatric transplant physicians when presented with identical scenarios involving adolescents and young adults. In the specific case of whether to recommend imatinib or transplantation for chronic phase CML, reluctance among pediatric transplant physicians to apply data derived from studies among adults to the treatment of older pediatric patients, or greater concern about unknown long-term effects of tyrosine kinase inhibitors, may help explain the observed differences in treatment recommendations. Differences in pediatric and adult decision making persisted in multivariate models that simultaneously adjusted for other physician and transplant center characteristics such as age, sex, center size, and center location.

Our data confirm that management of steroid-refractory acute and chronic GVHD is highly variable among both adult and pediatric physicians. Pediatricians tend to use higher dose steroids to treat steroid-refractory acute and chronic GVHD, and to wait longer before tapering steroids in chronic GVHD, than do adult transplant physicians. Older patients may have more complications with corticosteroids, such as myopathy and avascular necrosis of bone, leading their physicians to minimize dosing as soon as possible.

Several studies utilizing surveys have assessed practice variation among transplant centers. Wide practice variation has been noted in dimethylsulfoxide autologous cryopreservation protocols,⁸ approaches to prophylaxis and treatment of acute GVHD,⁹ definitions of steroid-refractory acute GVHD and salvage treatment regimens,¹⁰ infectious prophylaxis and compliance with published guidelines,¹¹ and diagnosis and management of chronic GVHD.¹² However, only Rutuu and colleagues¹³ have attempted to compare reported practices with actual patient outcomes. This group compared reported center practices for handling steroid-refractory acute GVHD with the actual outcomes of CML patients developing GVHD at the centers. They reported better outcomes when lower dose steroids were used for

initial acute GVHD treatment,¹³ consistent with findings from a randomized clinical trial.²⁹

We acknowledge several limitations of the data presented herein, and emphasize that this study was an exploratory analysis of practice variation within the field of HCT. First, because of difficulties in defining the denominator of eligible physicians, the true response rate to the survey was somewhere between 32% and 84%. Based on the CIBMTR's update of its database in 2007, many e-mail addresses we used were likely to have been defunct or to have reached individuals who were ineligible to participate. Although we requested that people opt-out, we do not have any true estimate of the actual denominator of eligible respondents reached. The literature suggests that an average physician survey achieves a response rate of 54%.³⁰ The second limitation is that we asked participants to answer based on what they "usually do with most" of their patients. Respondents were forced to choose their one best answer to the vignette without opportunity to learn additional clinical information. Although surveys are a common approach to measuring practice variation,^{17-19,31,32} they are one step removed from measuring actual practices.¹⁵ They do, however, have the advantage of ensuring that all physicians are working with identical data. Studies comparing vignettes with standardized patients (actors hired to impersonate real patients) and chart review suggest that vignettes can accurately reflect actual practice patterns and are much more cost-effective.^{33,34} The third limitation is that due to our concern about the length of the survey and ensuring responder anonymity, we can not elaborate further on many of our findings. For example, we did not collect data about institutional affiliations to explore whether medical decision making was consistent within practice groups. We do not know if transplant physicians were following institutional practice guidelines or practicing autonomously. Finally, and perhaps most importantly, several of the scenarios chosen were purposefully controversial without clear evidence to suggest one optimal approach.

Nevertheless, we believe this survey should encourage HCT physicians to question whether the degree of practice variation within the field is desirable. It also suggests there is significant selection bias in who is offered a HCT, in the type of HCT offered, and how post-HCT complications are managed, implying that a careful characterization of these factors is important in interpreting reported observational and single-institution data. Even randomized studies could be affected by practice variation if the randomization does not balance important clinical management characteristics.

Our results also have implications for clinical practice since they provide additional support for the observation that patients often receive different recommendations and treatment from different practitioners.^{4,35-37} It is important that practice variation be discussed with the patient who is “shopping around,” especially when such variation results from lack of data. Finally, we believe that the practice variation documented here should encourage the design and implementation of randomized clinical trials to address controversial areas of HCT practice. Where clinical trials are not feasible, rigorous observational data may provide the best available evidence to guide practice.

REFERENCES

1. Wennberg J, Gittelsohn A: Small area variations in health care delivery. *Science* 182:1102-1108, 1973
2. Grytten J, Sorensen R: Practice variation and physician-specific effects. *J Health Econ* 22:403-418, 2003
3. Kravitz RL, Greenfield S: Variations in resource utilization among medical specialties and systems of care. *Annu Rev Public Health* 16:431-445, 1995
4. Silberman G, Crosse MG, Peterson EA, et al: Availability and appropriateness of allogeneic bone marrow transplantation for chronic myeloid leukemia in 10 countries. *N Engl J Med* 331:1063-1067, 1994
5. Gratwohl A, Brand R, Apperley J, et al: Allogeneic hematopoietic stem cell transplantation for chronic myeloid leukemia in Europe 2006: Transplant activity, long-term data and current results: An analysis by the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Haematologica* 91:513-521, 2006
6. Gratwohl A, Baldomero H, Schwendener A, et al: Hematopoietic stem cell transplants for chronic myeloid leukemia in Europe—impact of cost considerations. *Leukemia* 21:383-386, 2007
7. Gratwohl A, Baldomero H, Frauendorfer K, et al: Results of the EBMT activity survey 2005 on hematopoietic stem cell transplantation: Focus on increasing use of unrelated donors. *Bone Marrow Transplant* 39:71-87, 2007
8. Windrum P, Morris TC, Drake MB, et al: Variation in dimethyl sulfoxide use in stem cell transplantation: A survey of EBMT centres. *Bone Marrow Transplant* 36:601-603, 2005
9. Ruutu T, Niederwieser D, Gratwohl A, et al: A survey of the prophylaxis and treatment of acute GVHD in Europe: A report of the European Group for Blood and Marrow, Transplantation (EBMT): Chronic Leukaemia Working Party of the EBMT. *Bone Marrow Transplant* 19:759-764, 1997
10. Hsu B, May R, Carrum G, et al: Use of antithymocyte globulin for treatment of steroid-refractory acute graft-versus-host disease: An inter-

national practice survey. *Bone Marrow Transplant* 28:945-950, 2001

11. Trifilio S, Verma A, Mehta J: Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: Heterogeneity of current clinical practice. *Bone Marrow Transplant* 33:735-739, 2004
12. Lee SJ, Vogelsang G, Gilman A, et al: A survey of diagnosis, management, and grading of chronic GVHD. *Biol Blood Marrow Transplant* 8:32-39, 2002
13. Ruutu T, Hermans J, van Biezen A, et al: How should corticosteroids be used in the treatment of acute GVHD? EBMT Chronic Leukemia Working Party: European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 22:614-615, 1998
14. Parsons SK, Hoorntje LE, Levine KJ, et al: Balancing efficacy with cost: Antiemetic control in the pediatric stem cell transplant (SCT) population. *Bone Marrow Transplant* 25:553-557, 2000
15. Lafata JE, Simpkins J, Schultz L, et al: Routine surveillance care after cancer treatment with curative intent. *Med Care* 43:592-599, 2005
16. Lindenauer PK, Pekow P, Gao S, et al: Quality of care for patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 144:894-903, 2006
17. Choy H, Shyr Y, Cmelak AJ, et al: Patterns of practice survey for nonsmall cell lung carcinoma in the U.S. *Cancer* 88:1336-1346, 2000
18. Ng AK, Li S, Neuberger D, et al: Factors influencing treatment recommendations in early-stage Hodgkin's disease: A survey of physicians. *Ann Oncol* 15:261-269, 2004
19. Taghian A, Jagsi R, Makris A, et al: Results of a survey regarding irradiation of internal mammary chain in patients with breast cancer: Practice is culture driven rather than evidence based. *Int J Radiat Oncol Biol Phys* 60:706-714, 2004
20. Katz SJ, Lantz PM, Janz NK, et al: Surgeon perspectives about local therapy for breast carcinoma. *Cancer* 104:1854-1861, 2005
21. United Nations World Macro regions and components 2007. <http://www.un.org/depts/dhl/maplib/worldregions/htm>
22. Schrezenmeier H, Passweg JR, Marsh JC, et al: Worse outcome and more chronic GVHD with peripheral blood progenitor cells than bone marrow in HLA-matched sibling donor transplants for young

patients with severe acquired aplastic anemia. *Blood* 110:1397-1400, 2007

23. Champlin RE, Perez WS, Passweg JR, et al: Bone marrow transplantation for severe aplastic anemia: A randomized controlled study of conditioning regimens. *Blood* 109:4582-4585, 2007
24. Bruno B, Rotta M, Patriarca F, et al: A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med* 356:1110-1120, 2007
25. Creutzig U, Reinhardt D: Current controversies: Which patients with acute myeloid leukaemia should receive a bone marrow transplantation? A European view. *Br J Haematol* 118:365-377, 2002
26. Chen AR, Alonzo TA, Woods WG, et al: Current controversies: Which patients with acute myeloid leukaemia should receive a bone marrow transplantation? An American view. *Br J Haematol* 118:378-384, 2002
27. Hasle H, Arico M, Basso G, et al: Myelodysplastic syndrome, juvenile myelomonocytic leukemia, and acute myeloid leukemia associated with complete or partial monosomy 7: European Working Group on MDS in Childhood (EWOG-MDS). *Leukemia* 13:376-385, 1999
28. Woods WG, Barnard DR, Alonzo TA, et al: Prospective study of 90 children requiring treatment for juvenile myelomonocytic leukemia or myelodysplastic syndrome: A report from the Children's Cancer Group. *J Clin Oncol* 20:434-440, 2002
29. Van Lint MT, Uderzo C, Locasciulli A, et al: Early treatment of acute graft-versus-host disease with high- or low- dose 6-methylprednisolone: A multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. *Blood* 92:2288-2293, 1998
30. Asch DA, Jedrzejewski MK, Christakis NA: Response rates to mail surveys published in medical journals. *J Clin Epidemiol* 50:1129-1136, 1997
31. Wusthoff CJ, McMillan A, Ablin AR: Differences in pediatric oncologists' estimates of curability and treatment recommendations for patients with advanced cancer. *Pediatr Blood Cancer* 44:174-181, 2005
32. Charles CA, Yee VS, Dusza SW, et al: Variation in the diagnosis, treatment, and management of melanoma in situ: A survey of US dermatologists. *Arch Dermatol* 141:723-729, 2005

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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33. Peabody JW, Luck J, Glassman P, et al: Comparison of vignettes, standardized patients, and chart abstraction: A prospective validation study of 3 methods for measuring quality. *JAMA* 283:1715-1722, 2000

34. Veloski J, Tai S, Evans AS, et al: Clinical vignette-based surveys: A tool for assessing physi-

cian practice variation. *Am J Med Qual* 20:151-157, 2005

35. Eagle KA, Goodman SG, Avezum A, et al: Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: Findings from the Global Registry of Acute Coronary Events (GRACE). *Lancet* 359:373-377, 2002

36. Hawley ST, Hofer TP, Janz NK, et al: Correlates of between-surgeon variation in breast cancer treatments. *Med Care* 44:609-616, 2006

37. Alexander KP, Newby LK, Bhapkar MV, et al: International variation in invasive care of the elderly with acute coronary syndromes. *Eur Heart J* 27:1558-1564, 2006

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