

Health Care Utilization by Adult Long-term Survivors of Hematopoietic Cell Transplant: Report from the Bone Marrow Transplant Survivor Study

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Abstract

The high intensity of therapy and prolonged immune suppression after hematopoietic cell transplantation (HCT) increase the risk of long-term complications and health care needs among survivors. The aim of this study was to evaluate the current status of health care utilization by long-term HCT survivors and to identify factors associated with lack of utilization. A total of 845 individuals who had undergone HCT between 1974 and 1998 at age 21 years or older and survived 2 or more years after HCT participated in the study. Health care utilization was assessed through a mailed questionnaire in three domains: general contact with health care system, general physical examination, and cancer/HCT-related visit. The median age at HCT was 38.2

years, and the median length of follow-up was 6.4 years. Overall, 98% of allogeneic and 94% of autologous HCT survivors reported medical contact 11+ years after HCT. Cancer/HCT-related visits decreased with increasing time from HCT (allogeneic HCT, 98-57%; autologous HCT, 94-63%). The prevalence of general physical examination increased with time (allogeneic HCT, 56-74%; autologous HCT, 72-81%). Primary care physicians provide health care for an increasing number of adult long-term survivors of HCT, emphasizing the need for increased awareness of the long-term follow-up needs of the HCT survivors by the health care providers. (Cancer Epidemiol Biomarkers Prev 2007;16(4):834-9)

Introduction

Hematopoietic cell transplantation (HCT) is used to treat a variety of malignant and nonmalignant disorders. Improved transplantation strategies and supportive care combined with a wider variety of stem cell sources have led to increased utilization of this therapeutic modality (1). Multiple factors, such as exposure to high-dose chemotherapy, prophylaxis/treatment of graft versus host disease (GVHD), sequelae of GVHD, and prolonged immune suppression place the survivors at increased risk of long-term adverse sequelae. Several disease-specific and therapy-related late effects have been described in HCT survivors (2-8), resulting in increased mortality, morbidity, and compromised health status (1, 2, 9, 10). This population is thus likely to have a higher need for utilization of the health care system for many years after their treatment.

Although several studies have evaluated the health care utilization by cancer survivors (11-14), there are no reports describing the pattern of health care utilization by transplant survivors. The goal of this study was to evaluate self-reported health care utilization by long-term HCT survivors and to identify risk factors associated with lack of utilization.

Materials and Methods

Patients. The Bone Marrow Transplant Survivor Study, a collaborative effort between the City of Hope Cancer Center

and the University of Minnesota, examines the long-term outcomes of individuals who have survived 2 or more years after undergoing HCT and compares them with nearest-age siblings. The current report is restricted to individuals who met the following eligibility criteria: (a) HCT between 1974 and 1998 at City of Hope Cancer Center/University of Minnesota; (b) 21 years or older at time of HCT; and (c) survival of 2 or more years after HCT irrespective of current disease status. The Human Subjects committee at the participating institutions approved the Bone Marrow Transplant Survivor Study protocol. Informed consent was provided according to the Declaration of Helsinki.

A 255-item mailed questionnaire was used to collect information from all participants. The questionnaire was designed to capture a wide range of information, including demographic characteristics, marital status, insurance coverage, education, income, employment, access and utilization of medical care, current health status, and concerns for future health. Detailed clinical information was obtained from the institutional medical records.

Outcome Measures. Health care utilization in the 2 years preceding the survey was assessed in three domains: (a) general contact with the health care system (medical contact); (b) general physical examination (GPE); (c) cancer/HCT-related visit: cancer/transplant-related medical visit with the transplant team or medical visit at a cancer center. These outcomes were not mutually exclusive. General or nonspecific medical contact was ascertained by asking the respondent if they had contact with a physician, nurse, or other health care provider in the 2 years before the survey. The contact could include a visit to the physician's office or a phone contact. GPE was defined as a self-report of a GPE within the 2 years before survey. To ascertain cancer/HCT-related visit, the respondents were asked how many of their visits were related to their previous cancer or HCT and whether any of these visits were

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at the cancer center. The actual language used in the questionnaire to construct these outcome variables is shown in Table 1. The content or additional details about the medical visits were not ascertained.

Analysis. Potential risk factors for absence of health care utilization within any one of the three domains were analyzed using unconditional logistic regression. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated for assessing the strength of association. Univariate analyses for all pertinent variables were first done to estimate relative risk individually. Stepwise regression was used to select important variables from those that approached statistical significance in the univariate analysis, and a P value of <0.10 was used as the selection criterion. Variables examined included sociodemographic variables [age at time of HCT, age at survey, gender, race and ethnicity (White, Hispanic, other), educational status, current insurance, and household income], clinical variables [length of time since HCT, primary diagnosis, conditioning regimen [total body irradiation (TBI) versus non-TBI based], presence of chronic GVHD (for allogeneic transplantation only), drugs used for prophylaxis and treatment of GVHD (exposure to cyclosporin A versus no exposure: for allogeneic transplantation only), risk of relapse at HCT (standard versus high risk)], current health status, and concerns for future health. Patients were considered to be at standard risk for relapse if HCT was done in first or second complete remission; all others were considered as high risk. The final multivariate model only included those variables that reached statistical significance. P values <0.05 were considered statistically significant and all P values quoted were two-sided. Statistical analysis of the data was done using Epilog plus (Epicenter Software, Pasadena, CA).

Results

Of the 1,258 patients eligible for participation in this study, 1,176 were successfully contacted with 845 (71.9%) agreeing to participate. Four hundred and twenty-eight study participants had received an allogeneic HCT, whereas 417 had received an autologous transplant. The demographic and clinical characteristics of the cohort are described in Table 2. Because of the differences in disease characteristics and therapeutic agents used for conditioning, and the risk for GVHD, analyses were done and results are presented for the entire cohort and also stratified by type of transplantation.

Compared with the 413 nonparticipants, the 845 HCT survivors who participated in this study were significantly more likely to be White (80.6% versus 73.1%, $P < 0.01$), were

older at time of HCT (39.0 versus 36.6, $P < 0.001$) and at time of survey (46.6 versus 45.0, $P = 0.006$), and had a shorter length of follow-up from HCT (median length 7.6 versus 8.4, $P = 0.003$). Furthermore, participants were more likely to have received TBI (78.5% versus 71.4%, $P = 0.007$) as part of conditioning when compared with the nonparticipants. Participants and nonparticipants did not differ in terms of sex, primary diagnosis, and risk of relapse at HCT.

Fifty-four percent of the participants were males, 81% were White, and 54% had been followed for >5 years since HCT. Forty-five percent of the participants were college graduates, 48% reported an annual household income greater than \$60,000, and 93% had health insurance coverage. Primary diagnoses included Hodgkin's lymphoma (9.7%), non-Hodgkin's lymphoma (23.2%), acute myeloid leukemia (22.2%), acute lymphoid leukemia (6.2%), chronic myeloid leukemia (26.4%), multiple myeloma (5.0%), and other diagnoses (4.1%). Seventy-nine percent of the participants had received TBI-based conditioning regimen, and 38% were at high risk of relapse at time of HCT. Twenty-one percent rated their current health status as fair or poor, and 5% were not concerned about their future health.

Compared with autologous HCT survivors, allogeneic HCT survivors were younger at HCT (mean 35.8 years old versus 42.2 years old, $P < 0.001$) and at survey (mean 44.4 years old versus 48.8 years old, $P < 0.001$). Furthermore, allogeneic HCT survivors were less likely to be White (75.9% versus 85.4%, $P = 0.002$), have a college degree (40.6% versus 50.2%, $P = 0.02$), report an income more than \$60,000 (44.9% versus 52.0%, $P = 0.04$), be at high risk of relapse at HCT (30.1% versus 46.5%, $P < 0.001$), and report concern about their future health (2.9% versus 6.8%, $P = 0.01$). However, they were more likely to be uninsured (8.3% versus 4.6%, $P = 0.04$), with longer duration of follow-up (mean = 8.6 years versus 6.7, $P < 0.001$), more likely to have received TBI-based conditioning regimen (88.8% versus 67.9%, $P < 0.001$), and more likely to rate their current health as fair/poor (23.4% versus 17.6%, $P = 0.05$; Table 2).

Prevalence of Health Care Utilization

Entire Cohort. Health care utilization as a function of years since transplantation for the entire cohort is shown in Fig. 1A. Ninety-seven percent of the survivors followed beyond 10 years reported medical contact. Although the prevalence of GPE increased from 65% at 2 to 5 years to 76% at 11+ years after HCT ($P_{\text{trend}} = 0.003$), the prevalence of cancer/HCT-related visit decreased from 96% at 2 to 5 years to 59% at 11+ years after HCT ($P_{\text{trend}} < 0.001$).

Table 1. Self-reported health care utilization by HCT survivors—definition of outcome measures

Outcome measures	Question	Response options	Absence of utilization
General contact with the health care system	During the last 2 y, which of the following health care providers (excluding dentists) did you see or talk to for medical contact?	Physician Nurse Chiropractor Physical therapist	No medical contact: if no to all responses
GPE	Some people get a physical examination from a doctor once in a while although they are feeling well and have not been sick. When was the last time you had a GPE when you were not sick?	Never Less than 1 y ago 1-2 y ago 3-4 y ago ≥ 5 y ago	No GPE: if never or had a GPE >3 y ago
Cancer/HCT-related visit	As you know, you were asked to participate in this study because you were once diagnosed with a cancer, leukemia, tumor, or similar illness and underwent bone marrow transplantation (BMT). How many of the visits to the physician were related to this previous illness or BMT? Where did you receive your health care?	0 time 1-2 times 3-4 times 5-6 times 7-10 times 11-20 times >20 times Oncology (cancer) center or clinic	No cancer/HCT-related visit: if none of the visits related to previous illness or HCT or did not receive health care at cancer center

Table 2. Demographic characteristics of the study cohort by type of transplant

	Entire cohort (n = 845)	Type of HCT	
		Autologous (n = 417)	Allogeneic (n = 428)
Age (y), median (range)			
Age at transplantation	38.2 (21.0-68.6)	42.9 (21.0-68.6)	35.2 (21.1-62.0)
Age at study participation	46.3 (23.3-73.0)	49.1 (23.3-73.0)	44.5 (24.2-65.5)
Gender, n (%)			
Male	460 (54.4)	222 (53.2)	238 (55.6)
Race, n (%)			
White	681 (80.6)	356 (85.4)	325 (75.9)
Hispanic	96 (11.4)	36 (8.6)	60 (14.0)
Other	68 (8.0)	25 (6.0)	43 (10.1)
Education, n (%)			
High school or less	146 (17.3)	65 (15.6)	81 (19.0)
High school and some college	314 (37.3)	142 (34.1)	172 (40.4)
College degree	382 (45.4)	209 (50.2)	173 (40.6)
Household income, n (%)			
≥\$60,000/y	387 (48.4)	205 (52.0)	182 (44.9)
\$20,000-59,999/y	307 (38.4)	148 (37.6)	159 (39.3)
<\$20,000/y	105 (13.1)	41 (10.4)	64 (15.8)
Current health insurance, n (%)			
Uninsured	54 (6.5)	19 (4.6)	35 (8.3)
Duration of follow-up (y), n (%)			
2-5	387 (45.8)	219 (52.5)	168 (39.3)
6-10	285 (33.7)	150 (36.0)	135 (31.5)
≥11	173 (20.5)	48 (11.5)	125 (29.2)
Primary diagnosis			
Hodgkin's lymphoma	82 (9.7)	79 (18.9)	3 (0.7)
Non-Hodgkin's lymphoma	196 (23.2)	172 (41.2)	24 (5.6)
Acute lymphoid leukemia	52 (6.2)	8 (1.9)	44 (10.3)
Acute myeloid leukemia	188 (22.2)	75 (18.0)	113 (26.4)
Chronic myeloid leukemia	223 (26.4)	22 (5.3)	201 (47.0)
Aplastic anemia	27 (3.2)	—	27 (6.3)
Other	77 (9.1)	61 (14.7)	16 (3.8)
Relapse risk at HCT, n (%)			
High risk	322 (38.2)	194 (46.5)	128 (30.1)
Conditioning regimen n (%)			
Total body irradiation	661 (78.5)	281 (67.9)	380 (88.8)
Chronic graft vs host disease			
Yes	—	—	260 (60.9)
Graft vs host disease prophylaxis/treatment			
Cyclosporin A	—	—	321 (75.0)
Current health, n (%)			
Fair/poor	173 (20.6)	73 (17.6)	100 (23.4)
Concerns for future health, n (%)			
Not concerned	40 (4.9)	28 (6.8)	12 (2.9)

Allogeneic HCT Survivors. Figure 1B illustrates the prevalence of health care utilization with time since allogeneic transplantation. Ninety-eight percent of allogeneic transplant survivors followed beyond 10 years reported medical contact. Although the prevalence of GPE increased from 56% at 2 to 5 years to 74% at 11+ years after HCT ($P_{\text{trend}} = 0.006$), the prevalence of cancer/HCT-related visit decreased from 98% at 2 to 5 years to 57% at 11+ years after HCT ($P < 0.001$).

Autologous HCT Survivors. Health care utilization as a function of years since autologous transplantation is shown in Fig. 1C. Ninety-four percent of the survivors followed beyond 10 years reported medical contact. Although the prevalence of GPE increased from 72% at 2 to 5 years to 81% at 11+ years after HCT ($P_{\text{trend}} = 0.30$), the prevalence of cancer/HCT-related visit decreased from 94% at 2 to 5 years to 63% at 11+ years after HCT ($P_{\text{trend}} < 0.001$).

Multivariate Analysis. Due to the high prevalence of reported medical contact, multivariate analyses for identification of factors associated with not reporting health care utilization were done only for GPE and cancer/HCT-related visits, and results are shown in Table 3.

Entire Cohort: GPE. Allogeneic transplant survivors were more likely to report absence of GPE in the 2 years before participation, when compared with autologous HCT survivors (OR, 1.72; 95% CI, 1.1-2.6). Patients followed longer than

5 years from HCT were less likely to report absence of GPE ($P_{\text{trend}} = 0.004$). Patients transplanted for acute lymphoid leukemia were less likely to report absence of GPE when compared with those transplanted for chronic myeloid leukemia (OR, 0.39; 95% CI, 0.2-0.9). Finally, survivors rating their current health status to be fair or poor were more likely to report absence of GPE (OR, 1.89; 95% CI, 1.3-2.7) when compared with those who rated their health status as good.

Entire Cohort: Cancer/HCT-Related Visit. Allogeneic transplant survivors were less likely to report absence of cancer/HCT-related visit when compared with autologous HCT survivors (OR, 0.49; 95% CI, 0.3-0.9). Compared with survivors of non-Hispanic White background, Hispanic survivors were less likely to report absence of cancer/HCT-related visit. Patients followed longer than 5 years from HCT ($P_{\text{trend}} < 0.001$) and those expressing a lack of concern about their future health (OR, 4.05; 95% CI, 1.8-9.3) were more likely to report absence of cancer/HCT-related visits. Those survivors rating their own health to be fair/poor were less likely to report absence of cancer/HCT-related visit (OR, 0.51; 95% CI, 0.3-0.97). Compared with patients transplanted for chronic myeloid leukemia, patients with a primary diagnosis of acute myeloid leukemia were more likely to report absence of cancer/HCT-related visits (OR, 2.07; 95% CI, 1.1-3.8).

Allogeneic HCT Survivors: GPE. Allogeneic HCT survivors rating their current health status to be fair or poor were more

likely to report absence of a GPE in the 2 years before the study (OR, 2.06; 95% CI, 1.3-3.4) when compared with those who rated their health status as good. Compared with patients with a primary diagnosis of chronic myeloid leukemia, patients with a primary diagnosis of acute lymphoid leukemia were less likely to reporting absence of GPE (OR, 0.32; 95% CI, 0.1-0.8), whereas patients with non-Hodgkin's lymphoma/Hodgkin's lymphoma were more likely to report absence of GPE (OR, 2.50; 95% CI, 1.1-5.95). Additionally, the survivors followed longer than 5 years after HCT were less likely to report absence of GPE (6-10 years from HCT: OR, 0.44; 95% CI, 0.3-0.8; 11+ years: OR, 0.54; 95% CI, 0.3-0.9).

Allogeneic HCT Survivors: Cancer/HCT-Related Visit. Time since HCT was associated with an increased likelihood of reporting absence of cancer/HCT-related visit (6-10 years since HCT: OR, 6.82; 95% CI, 1.9-2.5; 11+ years: OR, 23.82, 95% CI, 6.6-86.5; $P_{\text{trend}} < 0.001$). Survivors that reported lack of concern about future health were more likely to report absence of cancer/HCT-related visits (OR, 9.69; 95% CI, 2.1-45.3), and those who used cyclosporin A for GVHD prophylaxis or treatment were less likely to report absence of cancer/HCT-related visit (OR, 0.36; 95% CI, 0.2-0.7). Compared with non-

Hispanic Whites, Hispanics were less likely to report absence of cancer/HCT-related visit (OR, 0.16; 95% CI, 0.04-0.59).

Autologous HCT Survivors: GPE. Autologous HCT survivors exposed to TBI-based conditioning regimen were more likely to report absence of GPE in the 2 years before the study (OR, 1.64; 95% CI, 1.0-2.7).

Autologous HCT survivors: Cancer/HCT-Related Visit. Autologous HCT survivors followed longer than 5 years from HCT ($P_{\text{trend}} < 0.001$) and those expressing a lack of concern about their future health (OR, 2.92; 95% CI, 1.1-7.5) were more likely to report absence of a cancer/HCT-related visit. However, patients transplanted for Hodgkin's lymphoma or non-Hodgkin's lymphoma were less likely to report absence of cancer/HCT-related visit (Hodgkin's lymphoma: OR, 0.22; 95% CI, 0.1-0.6; non-Hodgkin's lymphoma: OR, 0.26; 95% CI, 0.1-0.6), when compared with those transplanted for acute myeloid leukemia.

Discussion

This study of 845 long-term HCT survivors shows that 98% report general medical contact, 71% have had a GPE, and 84% report a cancer/HCT-related visit in the 2 years preceding the study. Thus, almost all HCT survivors report medical contact within the 2 years preceding study participation, and although the prevalence of GPE increases with time since transplantation, that of the cancer/HCT-related visits declines. Allogeneic transplant survivors are more likely to report cancer/HCT-related visits when compared with autologous transplant survivors. Furthermore, Hispanics and other non-White minority populations are more likely to report cancer/HCT-related visits when compared with the Whites. Additionally, patients who report no concerns about their future health are less likely to report cancer/HCT visits when compared with those who are concerned about their future health. Finally, those patients who rate their health as fair or poor are more likely to report cancer/HCT-related visits and less likely to report GPEs when compared with those who rate their health as good.

Although there is paucity of data regarding health care utilization by transplant survivors, several studies have reported the health care utilization patterns observed in cancer survivors treated with conventional therapy (11-15). The health care utilization reported by adult survivors of childhood cancer (11) shows that the likelihood of reporting a cancer-related visit or GPE decreases significantly with time from cancer diagnosis. Lack of health insurance, male gender, age more than 30 years at time of study, and lack of concern for future health have been identified as significant risk factors for not reporting GPE, cancer-related visit, or a cancer center visit.

Nord et al. (16) described the self-reported significantly higher use of health care services in long-term survivors of adult onset cancer when compared with normal controls. Hewitt et al. (17) used National Health Interview Survey (1998-2000) data to compare health status and health care utilization of adult cancer survivors and individuals without cancer. Cancer survivors were significantly more likely to report being in fair or poor health; experience a psychological disability, limitations of activities of daily living, or functional limitations; and report being unable to work because of a health condition. Twice as many survivors of cancer compared with those without a history of cancer had visited a physician in the preceding year. Patients with psychological problems and functional limitations reported more visits.

Successful treatment of patients undergoing HCT should not be limited to the immediate post-HCT period but must include plans for risk-based follow-up and screening for potential late effects to enable survivors to reintegrate into the society and reach their maximum potential. This study shows that although the large majority of HCT survivors

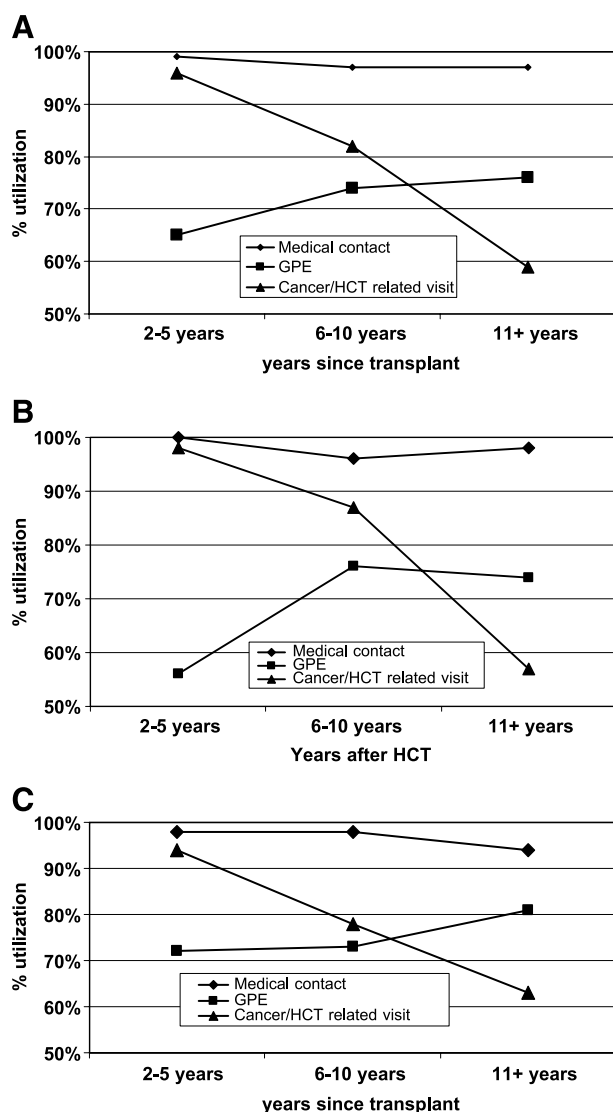


Figure 1. Trend over time for general contact (*Medical contact*), GPE, cancer/HCT-related visit after HCT: (A) for the entire cohort; (B) for allogeneic HCT only; (C) for autologous HCT only.

Table 3. Risk factors for absence of health care utilization reported by HCT survivors

Risk factors	Entire cohort		Allogeneic HCT		Autologous HCT	
	GPE	Cancer/HCT-related visit	GPE	Cancer/HCT-related visit	GPE	Cancer/HCT-related visit
Type of transplant						
Autologous	1.00	1.00				
Allogeneic	1.72 (1.1-2.6)	0.49 (0.3-0.9)				
Race						
Non-Hispanic White		1.00		1.00		
Hispanic White		0.23 (0.1-0.6)		0.16 (0.04-0.6)		
Others		0.67 (0.3-1.7)		0.66 (0.2-2.1)		
Follow-up years						
2-5	1.00	1.00	1.00	1.00		1.00
6-10	0.65 (0.5-0.9)	5.15 (2.7-9.7)	0.44 (0.3-0.8)	6.82 (1.9-24.5)		4.75 (2.3-10.1)
11+	0.57 (0.4-0.9)	19.06 (9.8-37.1)	0.54 (0.3-0.9)	23.82 (6.6-86.5)		9.16 (3.7-22.7)
<i>P</i> _{trend}	0.004	<0.0001	0.01	<0.001		<0.001
Concerns of future health						
Concerned		1.00		1.00		1.00
Not concerned		4.05 (1.8-9.3)		9.69 (2.1-45.3)		2.92 (1.1-7.5)
Current health status						
Good	1.00	1.00	1.00			
Fair/poor	1.89 (1.3-2.7)	0.51 (0.3-0.97)	2.06 (1.3-3.4)			
Exposure to cyclosporin A						
No exposure				1.00		
Exposed				0.36 (0.2-0.7)		
Exposure to TBI						
No exposure					1.00	
Exposed					1.64 (1.0-2.7)	

report medical contact within the 2 years preceding study participation, the prevalence of a transplant-related visit decreases with time from HCT, whereas the prevalence of general physical exam increases. These findings suggest that primary care physicians provide health care for a majority of this growing high-risk population. Although the risks of late effects of therapy increase with time, the number of survivors receiving care at a cancer center or from an oncologist or a transplant physician decrease with increasing time from HCT.

Zebrack et al. (13) described the survivors' lack of knowledge about the late effects of therapy and their lack of insurance on the one hand, and the lack of education of primary care providers about health problems of survivors as well as limited number of health care providers equipped to deal with survivors on the other hand, as barriers for optimum care of survivors.

Thus far, there has been little coordinated effort to enhance communications to provide risk-based care for HCT survivors. Limited education concerning this population of patients is incorporated into the primary care curricula. Furthermore, there is a paucity of reports regarding HCT survivors in primary care journals (11, 18). Finally, transplant survivors represent a small fraction of the patient population cared for by primary care physicians, which further compounds the lack of awareness regarding the specialized care needed by these patients. Health care provided to transplant survivors could be optimized by introducing interventions to educate survivors, ensuring smooth transition to primary care physicians, and enhancing and improving communication between transplant physicians and primary care physicians.

Models of care for long-term HCT survivors must be flexible to meet the specialized needs of this high-risk population, accommodating patients with a wide range of treatment exposures and risks for adverse long-term sequelae. Regardless of the model of care used, partnership with health care providers across a wide range of specialties is required to deliver optimal care. Internists, family medicine physicians, physician assistants, and nurse practitioners require ongoing education regarding the potential long-term effects for which the HCT survivors are at risk. There is therefore a need for standardized guidelines for follow-up and effective communication between transplant centers and

primary care physicians. The Center for International Blood and Marrow Transplant Research, European Group for Blood and Marrow Transplantation, and American Society for Bone Marrow Transplantation have developed recommendations to offer care providers suggested screening and prevention practices for autologous and allogeneic HCT survivors (19).

Although this is the first study of its kind, there are several limitations. Approximately one third of the eligible patients did not participate in the study. Although the participants and nonparticipants were similar in most respects, we could not assess the differences in late medical effects that could limit their participation. Health care utilization was determined by self-report and was not externally verified. Furthermore, the determination of transplant-related visit was based on patient's perception of the reason for the visit. Thus, there is likelihood of misclassification of visits. Finally, the number of ethnic minorities and uninsured patients is relatively small in this cohort and, hence, these results may not effectively represent such outcomes or associations in those populations.

In conclusion, although most survivors of HCT reported some contact with the health care system, the likelihood of transplant-related visit or cancer center visit decreases with time. The primary care physicians provide long-term health care for most of this high-risk population. Acceptance and utilization of standardized guidelines for long-term follow-up and ongoing and effective communication between transplant centers and primary care physicians are essential to optimize care for long-term transplant survivors.

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