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FREQUENCY OF ABNORMAL FINDINGS DETECTED BY COMPREHENSIVE CLINICAL EVALUATION AT ONE YEAR AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION

Stephanie J. Lee, MD, MPH[1], **Travis Seaborn**[1], **Frances J. Mao, BS**[1], **Susan C. Massey**[1], **Ngoc Q. Luu, BS**[1], **Mary A Schubert, ARNP**[2], **Jason W. Chien, MD, MS**[3], **Paul A. Carpenter, MBBS**[1], **Carina Moravec, ARNP**[2], **Paul J. Martin, MD**[1], and **Mary ED Flowers, MD**[1]

[1] Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA

[2] Long-Term Follow-Up Unit, Seattle Cancer Care Alliance, Seattle, WA

[3] Division of Pulmonary and Critical Care, Fred Hutchinson Cancer Research Center, Seattle, WA

Abstract

Consensus guidelines recommend a number of screening examinations for survivors following allogeneic hematopoietic cell transplantation (HCT) but the frequency of detecting abnormal findings is unknown. We reviewed medical records of 118 patients who had comprehensive, standardized evaluations at one year after allogeneic HCT at Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance. Abnormal findings were common, including moderate-severe pulmonary dysfunction (16%), fasting hyperlipidemia (56%), osteopenia (52%), osteoporosis (6%), and active chronic graft-versus-host disease (64%). Recurrent malignancy (4%) and chronic graft-versus-host disease (29%) were detected in previously unsuspected cases. Only 3% of patients had no abnormal findings. We conclude that comprehensive evaluation at one year after allogeneic HCT detects a high frequency of medical problems. Longer follow-up will be required to determine whether early detection and intervention affects late morbidity and mortality.

Keywords

Late effects; allogeneic hematopoietic cell transplantation; chronic graft versus host disease; recurrent malignancy; hypothyroidism; osteoporosis; immunity

INTRODUCTION

Observational studies document the spectrum of late effects seen in adults(1–8) and children (9,10) after allogeneic hematopoietic cell transplantation (HCT). Several position statements have provided recommendations about appropriate patient follow-up after allogeneic HCT.

Correspondence: Stephanie J. Lee, MD, MPH, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, D5-290, Seattle, WA, 98109 206-667-5160 (tel), 206-667-4134 (fax), sjlee@fhcrc.org.

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(11–14) Recommendations emphasize detection and management of procedure-related complications and other late effects among HCT survivors. For example, screening for secondary cancers and abnormalities of endocrine, cardiovascular, pulmonary, renal and hepatic function are advised. Clinicians are also encouraged to discuss psychosocial issues and general health maintenance. Subspecialist evaluations by dentists, ophthalmologists and gynecologists are encouraged.

The frequency with which these late effects and general health screening recommendations are followed, the likelihood of detecting abnormalities that result in medical interventions and the ultimate impact of compliance with these screening recommendations on the health of HCT survivors are unknown. For three decades, the Fred Hutchinson Cancer Research Center (FHCRC) Long-Term Follow-Up (LTFU) program has offered a comprehensive evaluation on site to allogeneic recipients at one year after HCT (Table 1). Because results of the evaluations are not comprehensively collected in a research database, we reviewed medical records for 118 one-year evaluations conducted for adults who had allogeneic HCT in 2005 to describe the frequency of abnormal evaluations.

STUDY DESIGN

All adult patients who had allogeneic HCT in 2005 at FHCRC/Seattle Cancer Care Alliance (SCCA) who were seen by the LTFU program one year later were eligible for study. The study was approved by the FHCRC Institutional Review Board. A single year was chosen for study because detailed retrospective chart review was required.

Summary letters from FHCRC and laboratory results from the one year LTFU evaluation were reviewed to collect data about medical history, current abnormal findings, treatment recommendations, vaccinations and immunity, and current medications. Data regarding the patients' pre-transplant medical status were not collected. Diagnoses of hyperlipidemia (elevated fasting cholesterol, triglycerides or LDL), thyroid abnormalities (abnormal thyroid stimulating hormone, free thyroxine or thyroxine), iron abnormalities (abnormal ferritin, serum iron, total iron binding capacity or transferrin saturation), and immunity (preimmunization titers against specific pathogens) were based on laboratory results. Diagnosis of recurrent malignancy was based on blood, urine and bone marrow studies, radiologic tests and tissue biopsies. Chronic GVHD was diagnosed primarily by clinical criteria.(15) Thirty charts (25%) were randomly selected for second abstraction to confirm accuracy of 20 key variables. The median number of abstraction errors was one (5%) with a range of 0–6 errors.

Medians and ranges are reported for continuous variables and percentages for categorical variables. The Wilcoxon rank-sum test was used to compare continuous variables and the Chi-square or Fisher's exact test was used to compare categorical variables.

RESULTS

Subject characteristics

Two hundred fifty eight adults underwent allogeneic HCT in 2005. Among these 113 died and 11 had recurrent malignancy before one year and did not return for LTFU evaluation. Of 134 patients who survived at least one year and were alive without active malignancy making them eligible to return for their comprehensive evaluation, 118 (88%) are included in this study. Sixteen eligible patients (12%) did not return for one year evaluation. There were no statistically significant differences in the age, gender, donor type, graft source, transplant number, conditioning regimen, or frequency of second transplants between patients who did or did not return for LTFU evaluation. Information on insurance coverage was not available,

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and it is possible that lack of insurance or limitations on return visits to the transplant center could differ between those who did and did not return.

The study cohort included 69 (58%) men, 47 (40%) patients who had reduced intensity conditioning, 62 (53%) who had HCT from an unrelated donor, 105 (89%) who received G-CSF mobilized peripheral blood grafts, and 18 (15%) who had second transplants. The median age at HCT was 47 years (range 19–69 years). Forty eight (41%) lived in Washington state. Most (n=102, 86%) spent 2–4 days in Seattle for testing and consultation as part of their LTFU evaluation while 16 (14%) brought results of diagnostic testing performed elsewhere. These outside test results were reviewed in lieu of testing at FHCRC. Patients were usually followed by their primary oncologists and generally not seen by the LTFU clinical service at FHCRC/SCCA between day 100 and one year, even if they live locally.

Medication usage

At the time of the one year LTFU evaluation, patients were taking a median of six systemic medications (interquartile range 4–9) (Table 2). Most (94%) were still taking prophylactic antibiotics while 71% were taking immunosuppressive medications (56% calcineurin inhibitors and 50% corticosteroids). Use of bisphosphonates (30%), hormonal therapies (27%) and antidepressive agents (26%) was common. Fifteen percent of patients were taking medication for diabetes and 13% taking thyroid hormone replacement. Thirty eight percent were taking anti-hypertensive agents (7% angiotension converting enzyme inhibitors or angiotensin II receptor blockers), and 9% were taking lipid-lower agents (7% HMG CoA reductase inhibitors). We did not collect information about medication usage before HCT.

Prevalence of problems and frequency of recommendations

Table 3 shows the prevalence of selected problems after HCT. Among the 106 (90%) patients who had no prior evidence of disease relapse after HCT, 4 (4%) were diagnosed with recurrent malignancy during the LTFU visit. Prior to the LTFU visit, 56% of patients had active chronic GVHD, 18% had inactive or resolved chronic GVHD, and 31% had no chronic GVHD. Of the 31 without prior chronic GVHD, 9/31 (29%) were diagnosed with chronic GVHD during the LTFU visit so that the overall prevalence of active chronic GVHD was 64%. Pulmonary function tests (PFTs) were available for 116 subjects. Only 26 (22%) had a normal modified lung function score (mLFS) according to forced expiratory volume first second (FEV1) and diffusing capacity of carbon monoxide (DLCO) adjusted for hemoglobin.(16) Seventy two (62%) had mild pulmonary dysfunction (mLFS 3–5), 16 (14%) had moderate dysfunction (mLFS 6–9), and 2 (2%) had severe pulmonary dysfunction (mLFS 10–12). Compared with PFTs before HCT (n=115), 56 (49%) did not change categories and 6 (5%) improved by at least one category. In contrast, 46% worsened by one (n=50, 43%) or two (n=3, 3%) categories.

Gynecologic exam results were available for 45 of 49 women (92%). Pap smears were abnormal (n=10) or insufficient (n=1) in 24%, and led to recommendations for retesting before 1 year for 6 women (13%) or interventions for 2 women (4%). Twenty five women had mammograms, and all were normal. Vulvovaginal chronic GVHD was diagnosed in 20 women (47%), judged to be mild in 12 (29%), moderate in 5 (11%) and severe in 3 (7%). Overall, 26 of 45 women (58%) had one or more abnormal gynecologic findings leading to recommendations for altered screening schedules, therapeutic interventions, or medication changes in 20/26 (77%).

Only 4 patients (3%) had no abnormal findings. Most had two (n=29, 25%) or three (n=40, 34%) abnormal findings. The median number of treatment recommendations provided by FHCRC was 2 (n=50, 42%, interquartile range 2–3); only 1 patient (1%) did not receive a new recommendation after the LTFU evaluation. Active chronic GVHD and abnormal bone mineral

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density were the major problems that resulted in a dose change or new medication for affected patients whereas moderate-severe pulmonary dysfunction usually led to recommendations for more frequent pulmonary function testing. Abnormal laboratory studies (iron tests, fasting lipids and thyroid function tests) were least likely to result in treatment or monitoring changes. There was no statistical difference in the frequency of abnormal findings or treatment recommendations between patients who had reduced intensity or myeloablative conditioning.

Vaccination and immunity

Almost all patients received routine immunizations during the one year LTFU visit. Some physicians did not give immunizations if patients were currently ill or were known to have very low B cell numbers, although this practice was not standardized. Lack of protective antibody was documented for pneumococcus (45%), haemophilus influenza B (79%), tetanus (64%), and hepatitis B (74%); additional doses of at least one vaccine were recommended for 95% of patients.

DISCUSSION

Although our patients were all evaluated at approximately one year after HCT, our results are consistent with the literature regarding the overall incidence of late effects. Specifically, the rates of osteoporosis, osteopenia, hyperlipidemia, diabetes, gynecologic abnormalities and pulmonary function deficits are similar to other reports of survivors at later times after HCT.(2–4,6,7,9,17,18) Recurrent malignancy (4%) and chronic graft-versus-host disease (29%) were detected in previously unsuspected cases. Detection of new cases of chronic GVHD was not due to implementation of the new NIH Consensus Criteria, since the new standards are more restrictive than previous definitions.(15)

Several problems such as hyperlipidemia, iron test abnormalities, and thyroid function abnormalities were less likely to be discussed in the medical records or to generate a treatment recommendation. We hypothesize that physicians may have thought these laboratory abnormalities would resolve with time, or they may have been reluctant to recommend a new medication or intervention given the number of medications already taken by patients. Reports of late cardiovascular and other complications after allogeneic HCT suggest that more aggressive management of laboratory abnormalities may be warranted.(8,17)

The high rate of abnormal findings in our study suggests it is reasonable to use the one year anniversary of the graft infusion as a simple and easily remembered reminder to conduct a comprehensive evaluation. In fact, earlier screening may be warranted for some conditions where interventions can be applied within the first post-transplant year. Our experience is that use of the transplant anniversary date helps physicians track scheduled screening examinations and ensures that recommended testing is completed. Testing can be done by the transplant center or by the patient’s oncologist or primary physician.

Our study identified some routine tests that do not appear to be justified based on clinical use of the information. For example, routine chest x-rays, Schirmer’s tests and skin biopsies appeared to have little effect on treatment and monitoring recommendations unless supported by clinical symptoms.(14) Therefore, these tests would be better applied to symptomatic patients or situations where there is a defined clinical or research question.

Limitations of this study include the retrospective design and the assessment of practices in a single year at a single institution that might not be representative of other time periods or other institutions. We reviewed chart notes and electronic medical records including laboratory data, but these sources may not have fully captured medical problems, medical decision-making and physician recommendations. Sixteen patients (12%) did not return for LTFU evaluation.

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Although we did not identify any differing characteristics, these patients may have had their LTFU evaluations locally or differ in important ways from the returning cohort. For example, patients with no apparent transplant-related medical problems at one year might have felt that there was no need to return for a comprehensive evaluation.

We conclude that routine comprehensive LTFU evaluation at one year after allogeneic HCT detects a high frequency of medical problems requiring intervention or adjustment of therapy. While the ultimate effect on health outcomes is unknown, our findings suggest that systematic evaluation as early as one year after HCT is an important part of early detection and monitoring for late effects. Continued longitudinal study of this group of patients will be required to determine whether serious late effects and late treatment-related mortality can be prevented through continued screening and appropriate early interventions.(19,20)

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Table 1

Routine one year comprehensive evaluation at Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Category	Evaluations
History and physical exam	Chronic GVHD focused review of systems and examination Complete skin examination Range of motion testing, if indicated Weight, height, vital signs, medical photographs List of all medications and supplements
Laboratory testing	Complete blood cell count with differential Reticulocyte count Comprehensive chemistry panel Fasting lipid panel Virology screen (hepatitis, CMV) Immunization titers Endocrine evaluations (thyroid, sex hormones) Iron tests Immunosuppressive drug levels ABO typing (if ABO mismatched) Chimerism testing
Other studies	Bone marrow aspirate and biopsy Skin biopsy Pulmonary function tests Schirmer's test Dual energy X-ray absorptiometry Chest Xray (chest CT if indicated)
Secondary cancer screening	Mammogram (if > 35 years) Pap smear (if > 21 years or sexually active) Prostate specific antigen (if > 45 years) Colonoscopy (if > 50 years) Stool for occult blood (if > 40 years)
Subspecialist exams	Ophthalmology Oral Medicine (dentist) Gynecology

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Table 2

Medication usage at one year after allogeneic transplantation in 118 patients

	N (%)		N (%)
Ant-infective agent	111 (94)	Hormone replacement therapy	32 (27)
Calcineurin inhibitor	66 (56)	Anti-depressive agent	31 (26)
Corticosteroid	59 (50)	Diabetes medication	18 (15)
Anti-hypertensive agent	38 (32)	Thyroid replacement	15 (13)
Bisphosphonate	35 (30)	Lipid-lowering agent	11 (9)

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Table 3

Prevalence of abnormal findings and frequencies of recommendations at one year after allogeneic transplantation

		Recommendations for affected patients		
Problem	**Prevalence**	**Continuation of current management**	**Dose change, new medication, or change in monitoring schedule**	**No recommendation or no discussion in medical records**
Abnormal iron tests	71%	24%	17%	59%
Active chronic GVHD	64%	19%	79%	2%
Abnormal gynecologic finding	58%	28%	77%	0%
Elevated fasting lipid levels	56%	38%	18%	44%
Osteopenia + osteoporosis	52% + 6%	42%	44%	14%
Abnormal thyroid tests	22%	52%	16%	32%
Moderate-severe pulmonary dysfunction	16%	22%	78%	0%
Recurrent malignancy	4%[1]	0%	100%	0%

[1] Of patients without prior evidence of disease