Recovery and Long-term Function After Hematopoietic Cell Transplantation for Leukemia or Lymphoma

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Context Hematopoietic cell transplantation (HCT) is an effective and widely used treatment for hematologic malignancies. The rate and predictors of physical and emotional recovery after HCT have not been adequately defined in prospective long-term studies.

Objective To examine the course of recovery and return to work after HCT.

Design, Setting, and Patients Prospective, longitudinal cohort study at a US academic center specializing in HCT. Function was assessed from pretransplantation to 5-year follow-up for 319 adults who had myeloablative HCT for treatment of leukemia or lymphoma and spoke English. Of the 99 long-term survivors who had no recurrent malignancy, 94 completed 5-year follow-up.

Main Outcome Measures Physical limitations, return to work, depression, and distress related to treatment or disease were evaluated before transplantation, at 90 days, and at 1, 3, and 5 years after HCT.

Results Physical recovery occurred earlier than psychological or work recovery. Only 21 patients (19%) recovered on all outcomes at 1 year. The proportion without major limitations increased to 63% (n = 57) by 5 years. Among survivors without recurrent malignancy, 84% (n = 74) returned to full-time work by 5 years. Patients with slower physical recovery had higher medical risk and were more depressed before HCT ($P \leq .001$). Patients with chronic graft-vs-host disease ($P = .01$), with less social support before HCT ($P = .001$), and women ($P < .001$) were more depressed after transplantation. Transplant-related distress was slower to recover for allogeneic transplant recipients and those with less social support before HCT ($P \leq .01$). Patients who had more experience with cancer treatment before beginning HCT had more rapid recovery from depression ($P = .04$) and treatment-related distress ($P = .009$).

Conclusions Full recovery after HCT is a 3- to 5-year process. Recovery might be accelerated by more effective interventions to increase work-related capabilities, improve social support, and manage depression.

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SURVIVAL RATES AFTER MYELOABLATIVE hematopoietic cell transplantation (HCT) have improved considerably during the past 30 years.[1] The growing population of patients who have survived this treatment has intensified the need to determine the course of recovery and to identify risk factors for less favorable functional outcomes. Improved understanding of recovery will facilitate more accurate informed consent, permit better planning by patients, families, and medical teams, and enable the design of interventions to improve functional recovery.

Medical complications of HCT have been well documented and include chronic graft-vs-host disease (GVHD), recurrent infection, pulmonary complications, premature menopause, cataracts, osteoporosis, avascular necrosis, infertility, recurrent malignancy, and secondary malignancy.[2-10] Cross-sectional studies have documented functional and mental health from 1 to 10 years after transplantation but have not described the course of recovery or identified pretransplantation factors that predict recovery.[11-19] Other studies have been limited by lack of pretransplantation baseline assessment,[20] shorter follow-up,[21-25] or small sample size when follow-up extends to 3 years.[26,27]

We conducted a prospective, longitudinal study to examine recovery of physical and mental health and return to work after HCT for treatment of leukemia or lymphoma. Assessments began before the transplantation and continued for 5 years to identify pre-

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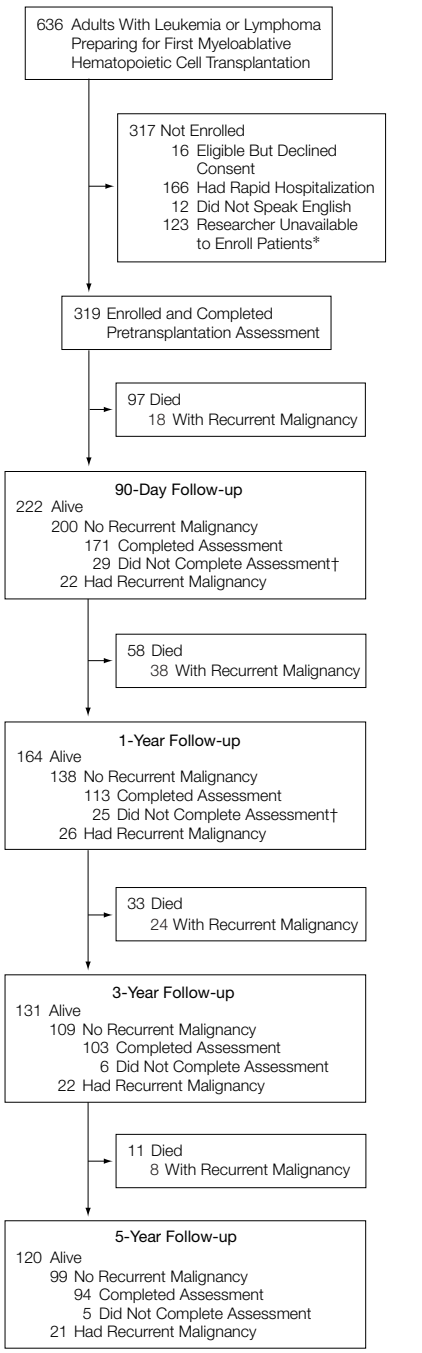
Figure 1. Flow of Participation in the Study



*Only 1 researcher assessed patients and sought consent for participation. When this researcher was unavailable, new patients could not be enrolled.

†Assessments at 90 days and 1 year were performed at the transplant center; assessments at 3 and 5 years were mailed to patients' homes.

transplantation characteristics associated with outcomes after HCT. Based on previous research, we hypothesized that physical and emotional recovery would occur by 1 year, autologous transplantation recipients would recover more rapidly than allogeneic transplant recipients, and risk factors for slower or poorer recovery would include higher medical risk as indicated by relapsed disease at the time of transplantation, history of extensive chronic GVHD, and pretransplantation depression.

METHODS

Patients and Procedures

A total of 335 adults who were preparing for a first myeloablative HCT for leukemia or lymphoma were invited to participate in this study. Eligible participants were at least 18 years old, had sufficient English language proficiency to complete the assessments, and were available to complete the baseline assessment in the ambulatory clinic before the transplantation. Each patient provided written informed consent. Sixteen patients declined to participate. The transplant center institutional review board and scientific review committee approved the study procedures, the consent form, and assessments. Pretransplantation, 90-day, and 1-year self-administered assessments were conducted in the ambulatory clinic with a researcher available to answer questions. The 3- and 5-year repeated assessments were conducted by mail with a researcher available by toll-free telephone line for questions. The researcher called to follow up with participants who did not return forms within 3 weeks. All participants were contacted for follow-up until 5 years, death, or the development of recurrent malignancy, whichever occurred first.

Outcomes

Primary Outcomes. Three self-report instruments were used to evaluate outcomes: the ambulation subscale of the Sickness Impact Profile (SIP)[28] as a measure of physical limitations, the Beck Depression Inventory (BDI)[29] as a measure of clinical depression, and Cancer Treatment Distress scale[30] as a measure of distress or worry specific to the transplantation and associated complications. At each time point, participants defined their work situation. At 3 and 5 years, participants were asked to provide a date of return to work, which was operationally defined as either full-time work outside the home, full-time school, or part-time school coupled with part-time work.

In this sample, the SIP ambulation subscale correlated highly with the entire SIP physical function subscale across time (r=0.74 to 0.91) and encompassed the major areas of long-term difficulty for transplant recipients over time. As a result, the shorter ambulation subscale was used to assess physical limitations. Continuous SIP scores were used for descriptive analyses, but because the distribution showed strong positive skewing after 90 days (1-year mean=2.53; range, 0-37.41), we used a dichotomous score for statistical models. Patients with scores more than 1 SD above age- and sex-adjusted population norms were considered to have clinically meaningful physical limitations.

Higher scores on the BDI indicated greater severity of depression. General population norms[29] were used to define categories of no depression (<10), mild depression (10-15), moderate depression (16-21), and severe depression (>21).

For the Cancer Treatment Distress measure, 27 items such as "nausea or vomiting," "possibility of relapse," and "being a burden to other people" were rated for the extent to which they caused distress or worry (0=no distress, 3=severe distress). A mean score was calculated with a possible range of 0 to 3. This distress measure has predicted pain, nausea, and distress among transplant recipients during treatment better than generalized measures of anxiety or depression.[30,31]

Medical Records Extraction of Risk Factors. Medical data were analyzed as risk factors for outcomes and were collected from the clinical research database, including diagnosis, conditioning regimen, history of treatment before HCT, stem cell donor (autologous vs allogeneic related or unrelated), date of

onset of clinical extensive chronic GVHD, and dates of recurrent malignancy and death. Pretransplantation risk categories were assigned with 3 levels depending on diagnosis and disease status.[32] Chronic myeloid leukemia in chronic phase was classified as low risk, acute leukemia or lymphoma in remission and chronic myeloid leukemia in accelerated phase were classified as moderate risk, and acute leukemia or lymphoma in relapse and chronic myeloid leukemia in blast crisis were classified as high risk.

Self-reported Risk Factors. Income (≤$49 999 vs ≥$50 000), marital status, and education before HCT (<4-year college degree vs ≥4-year college degree) were treated as dichotomous variables. The Social Support Inventory[33] was administered at baseline as a possible predictor of outcomes. This instrument was not administered at the posttransplantation time points simply to minimize patient burden. Scores reflected overall satisfaction with multiple kinds of support (advice, major and minor assistance, love, encouragement, and understanding). Ratings were made on 7-point scales for each type of support, with higher numbers indicating greater satisfaction.

Statistical Methods

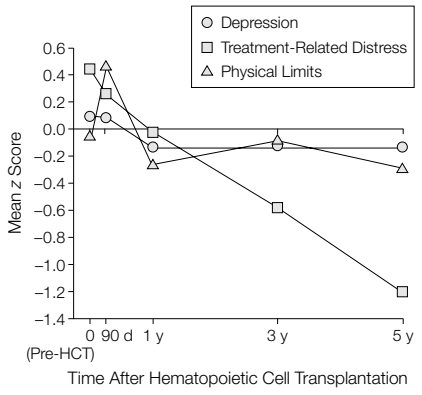
Descriptive and inferential analyses were performed using SPSS version 10.0 (SPSS Inc, Chicago, Ill) and Stata version 6.0 (Stata Corp, College Station, Tex). To compare recovery rates across the 3 primary outcomes, scores for physical function, depression, and treatment distress were standardized to the same scale using *z* scores derived from the entire data set. Generalized estimating equations were used to test for differences between trajectories of these outcomes. This analysis method accounted for the statistical dependence of repeated observations over time and permitted inclusion of results for participants who did not complete all assessments.[34] Generalized estimating equations were also used to develop statistical models of association between baseline characteristics and out-

Table 1. Pretransplantation Patient Characteristics

	No. (%)		
	Not Consenting to Participate (n = 317)	Consenting to Participate (n = 319)	Consenting and 5-Year Survivor Without Recurrence (n = 99)
Age, y			
Mean (SD)	35 (10.08)	36 (9.82)	36 (9.34)
Range	18-62	18-62	19-59
Sex			
Male	186 (59)	180 (56)	52 (53)
Female	131 (41)	139 (44)	47 (47)
Race/ethnicity			
White, non-Hispanic	284 (90)	303 (95)	93 (94)
Nonwhite or Hispanic	33 (10)*	16 (5)	6 (6)
Education			
College or postgraduate degree		131 (41)	45 (46)
No college degree		175 (55)	51 (52)
Unknown	317 (100)	13 (4)	3 (3)
Income, annual $			
≤49 999		182 (57)	60 (61)
≥50 000		111 (35)	33 (33)
Unknown	317 (100)	26 (8)	6 (6)
Marital status			
Married/cohabiting		211 (66)	65 (66)
Not married at time of transplantation		98 (31)	32 (32)
Unknown	317 (100)	10 (3)	2 (2)
Diagnosis			
CML, chronic phase	60 (19)	88 (28)	43 (44)*
CML, accelerated or blast crisis	41 (13)	45 (14)	9 (9)
Acute leukemia in remission	41 (13)	57 (18)	16 (16)
Acute leukemia in relapse or de novo	104 (33)*	63 (20)	11 (11)*
Lymphoma in remission	13 (4)	20 (6)	9 (9)
Lymphoma in relapse	58 (18)	46 (14)	11 (11)
Pretransplantation medical risk†			
Low	60 (19)	88 (28)	43 (44)*
Moderate	73 (23)	104 (33)	33 (33)
High	184 (58)*	127 (40)	23 (23)*
Stem cell donor			
Autologous	67 (21)	55 (17)	18 (18)
Allogeneic, related donor	196 (62)	222 (70)	69 (70)
Allogeneic, unrelated donor	54 (17)	42 (13)	12 (12)
Regimen included total body irradiation			
Yes	258 (81)	276 (87)	90 (91)
No	59 (19)	43 (13)	9 (9)
Radiation therapy history before transplantation			
Yes		55 (17)	11 (11)*
No		244 (77)	85 (86)*
Unknown	317 (100)	20 (6)	3 (3)
Chemotherapy before transplantation			
Yes		255 (80)	77 (78)
No		52 (16)	18 (18)
Unknown	317 (100)	12 (4)	4 (4)
Primary outcomes at pretransplantation			
Physical limits (SIP), %		25	18*
Beck Depression Inventory, mean (SD)‡		7.67 (5.92)	7.07 (5.45)
Cancer Treatment Distress, mean (SD)‡		1.12 (0.52)	1.07 (0.44)
History of school or work outside the home, %		88	92

Abbreviations: CML, chronic myelogenous leukemia; SIP, Sickness Impact Profile ambulation subscale.
*$P<.05$ comparison for the consenting cohort vs those not consenting or vs the cohort of consenting 5-year survivors.
†See the "Methods" section for definitions of medical risk.
‡For the Beck Depression Inventory, scores were: no depression (<10), mild depression (10-15), moderate depression (16-21), and severe depression (>21). For the Cancer Treatment Distress scale, 27 items were measured on a 0-3 scale.

Figure 2. Mean *z* Scores for the Primary Outcomes



Scores for each outcome were standardized with *z* scores across the entire data set to permit comparisons between different outcome measures. HCT indicates hematopoeitic cell transplantation.

comes, using models that included time, risk factor, and time × risk factor interaction terms. The model for physical function used the dichotomous version of that variable and assumed correlated binomial errors; models for depression and distress assumed correlated normal errors.

All models tested the same 15 risk factors: stem cell donor (autologous vs allogeneic), medical risk category, clinical extensive chronic GVHD, diagnosis, total body irradiation in the conditioning regimen, history of radiation therapy before transplantation, history of chemotherapy before transplantation, age, sex, education, income, marital status, and pretransplantation levels of physical limits, depression, and treatment distress. A parsimonious model for each outcome was calculated via forward stepwise entry to the model for risk factors with either a main effect or interaction with time significant at the $P<.05$ level. Cumulative incidence and Cox proportional hazards estimates were used to examine return to full-time work using the same risk factors. These analyses were conducted with the subsample of patients who had a history of work or school outside the home prior to transplantation.

RESULTS

Patient Characteristics

FIGURE 1 displays the consenting and follow-up of eligible patients. The lower rates of response at 90 days and 1 year resulted from the fact that assessments were conducted at the transplant center with those on site for follow-up, whereas the 3- and 5-year assessments were administered by mail to all survivors without recurrent malignancy. Among patients who completed the 1-year assessment, residual treatment distress was lower for those who completed the 90-day assessment than for those who did not ($P=.001$), but the 2 groups had no significant differences in physical limitations or depression. Among survivors who completed the 3-year assessment, no significant differences in any of the outcome measures were detected between those who completed the 90-day assessment and those who did not.

TABLE 1 summarizes patient demographic and clinical characteristics as a function of cohort: those in the cohort consenting to participate (n=319), those not consenting to participate (n=317), and those consenting and in the subgroup surviving to 5 years without recurrent malignancy (n=99 of the 319 patients). Based on comparisons between those consenting vs not consenting to participate and between those consenting and the subgroup who survived to 5 years, these groups did not differ in most characteristics. Five-year survival was 33% in the consenting sample and 21% in the not consenting sample (log-rank $P<.001$). Patients not consenting vs consenting were more likely to have diagnoses of acute leukemia in relapse ($P<.001$) and were more likely to be high risk ($P<.001$). The cohort not consenting had a higher number of nonwhite or Hispanic patients ($P=.004$). Among patients not consenting, 12 nonwhite or Hispanic patients were not eligible because they did not speak English; the cohort difference was not significant when these patients were excluded from the analysis.

As expected, the 5-year survivor cohort was generally medically healthier than the cohort of all consenting patients. The cohort of all consenting patients more often had previous radiation therapy ($P=.03$), were more likely to be in relapse before transplantation ($P=.001$), and were more frequently at high medical risk ($P<.001$) than the subgroup of 5-year survivors. In comparing outcomes between all consenting patients and those who were 5-year recurrence-free survivors, the 2 groups had few differences (Table 1).

Changes Over Time

The trajectories of physical limitations, depression, and treatment distress varied over time and differed from each other ($P<.001$) in generalized estimating equation analysis (FIGURE 2). Physical limitations reached a peak at 90 days after HCT, followed by improvement at 1 year and no further significant change at 3 and 5 years. Before the transplantation, 25% of patients (n=81) reported major physical limitations. The proportion increased to 44% (n=76) of survivors at 90 days and then decreased to 12% (n=14) at 1 year. At 3 and 5 years, respectively, 22% and 18% of survivors (n=23 and 16) reported major physical limitations. Treatment distress was high before HCT and at 90 days after the transplantation and then decreased steadily at each subsequent assessment. Depression changed less dramatically over time. Mean scores at 90 days were unchanged from baseline, while scores at 1, 3, and 5 years were lower, with no change after the first year. Thus, both physical limits and depression analyses confirmed our first hypothesis that most recovery would occur by 1 year, but treatment distress did not recover in this time frame and continued to resolve over 3 to 5 years.

Because averages can be deceiving, we defined clinically meaningful rates of distress and depression for further analysis. We used the 5-year mean score plus 1 SD as the threshold for clinically meaningful distress. According to this standard, 79% of survivors (n=84) remained distressed at 1 year, 42% (n=35) at 3 years, and 13% (n=11) at

5 years. We used general population norms to define the threshold for depression in this sample. At 90 days, 33% (n=102) reported depressive symptoms, whereas at 5 years 19% (n=18) had depressive symptoms. Most of those with symptoms had mild depression. At each assessment, 7% to 11% of patients had moderate to severe depression. Among the 188 patients who had at least 2 assessments, 78% (n=146) never had moderate to severe depression, 21% (n=39) had moderate to severe depression at some (but not all) assessments, and 1% (n=2) had moderate to severe depression at all assessments. An additional 31% (n=58) were never moderately or severely depressed, but had mild depressive symptoms at 1 or more assessments.

Table 2. Logistic Regression Predicting Physical Limitations Over Time (n = 295)*

Risk Factor	OR (95% CI)†	*P* Value	*P* Value for Overall Test
Time			
Pretransplantation	1.00		
90 Days	12.63 (5.57-28.63)	<.001	
1 Year	2.72 (1.01-7.34)	.048	<.001
3 Years	2.88 (1.08-7.68)	.04	
5 Years	2.38 (0.71-8.06)	.16	
History of radiation therapy			
No	1.00		
Yes	1.94 (1.14-3.30)		.01
Pretransplantation depression, per point increase	1.09 (1.05-1.13)		<.001
Medical risk by time interaction, relative to low risk‡			
Pretransplantation	3.91 (1.70-8.99)	<.001	
90 Days	0.14 (0.05-0.37)	<.001	
1 Year	0.07 (0.02-0.28)	<.001	<.001
3 Years	0.28 (0.09-0.88)	.03	
5 Years	0.26 (0.06-1.06)	.06	

Abbreviations: CI, confidence interval; OR, odds ratio.
*Variables that predicted physical limitations in univariate analyses ($P<.10$) but were not retained in the final model included pretransplantation distress and diagnosis. Variables that did not predict physical limitations over time in univariate models included patient age and sex, allogeneic vs autologous transplant, total body irradiation, history of chemotherapy, chronic graft-vs-host disease, education, marital status, income, and pretransplantation social support.
†For risk factors with only main effects, the OR indicates difference from the reference group. For risk factors with interactions with time, the pretransplantation OR represents the difference between groups at pretransplantation. The 90-day to 5-year ORs represent differences between groups in relative change from pretransplantation.
‡Moderate- and high-risk categories were combined after analysis indicated that they did not differ in predicting outcome vs the low-risk category.

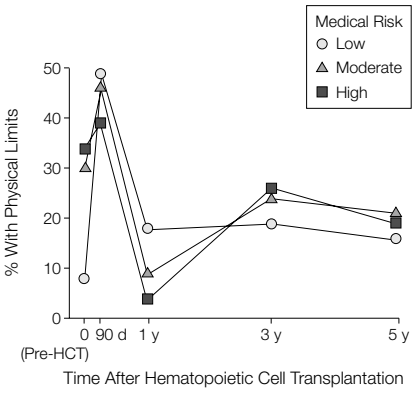
Predicting Outcomes

Analyses only partially confirmed that risk factors for poorer or slower recovery would include allogeneic transplant, higher medical risk, clinical extensive chronic GVHD, and depression. Risk factors for physical limits included depression, higher medical risk, and a history of radiation therapy before transplantation (TABLE 2). Before HCT, physical limitations were reported more frequently among patients in the moderate or high medical risk categories than among those in the low-risk category. After transplantation and long-term, the groups were similar in rates of patients reporting physical limits and different from their relative rates of impairment before transplantation (FIGURE 3). Throughout follow-up, physical limitations occurred more often among patients who were depressed before HCT than among those who were not depressed (FIGURE 4). A history of radiation therapy before transplantation also increased the risk for long-term physical limitations. Contrary to our hypotheses, neither allogeneic transplant nor chronic GVHD predicted physical limits.

Patients with chronic GVHD and women reported more depression. Similarly, those with no history of chemotherapy before their transplantation and with lower satisfaction with support before HCT reported more depression across time (TABLE 3). If patients had physical limits before HCT, they were more depressed before transplantation but not afterward. At 90 days, depression had declined more in patients with a history of radiation therapy before starting HCT treatment than in patients without previous radiation therapy. In relation to our hypotheses, analyses confirmed that patients with chronic GVHD reported more depression. However, contrary to our hypotheses, there was no difference in depression between allogeneic and autologous transplant recipients or between those with higher or lower medical risk.

Risk for treatment-related distress was greater over time for patients who had lower satisfaction with support before the HCT, those who had no history of chemotherapy before they received transplant chemotherapy, and in acute leukemia patients vs those with chronic leukemia or lymphoma (TABLE 4). Confirming our second hypothesis, distress declined more rapidly between pretransplantation and 3 years in patients who received autologous vs allogeneic stem cells, al-

Figure 3. Respondents With Physical Limitations Over Time, According to Baseline Medical Risk Category

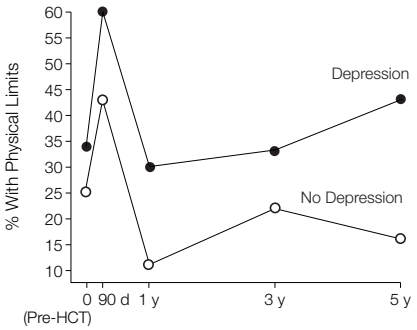


Patients with scores ≥1 SD above age- and sex-adjusted norms were classified as having physical limitations. Medical risk is defined in the "Methods" section. $P<.001$ for interaction of risk × time. HCT indicates hematopoeitic cell transplantation.

though the pattern of recovery from distress was otherwise similar (FIGURE 5. Women reported more distress before HCT and remained at a higher rate than men until they declined more rapidly in distress between 3 and 5 years. Patients with a college or postgraduate education were slower to decline in distress. Contrary to our third hypothesis, medical risk and extensive chronic GVHD were unrelated to treatment distress within or across time.

Other risk factors tested did not significantly predict the primary outcomes. Factors unrelated to any of the outcomes tested included age, income, marital status, and whether a patient received total body irradiation as part of the treatment regimen. Cohort diversity was not adequate to consider race or ethnicity as a predictor of outcomes.

Figure 4. Respondents With Physical Limitations Over Time, According to Presence or Absence of Depressive Symptoms at Baseline



Beck Depression Inventory scores ≥10 based on general population norms were classified as positive for depression. $P<.001$ for comparison between groups. HCT indicates hematopoeitic cell transplantation.

Return to Work

Eighteen of the 281 patients who had a history of school or work outside the home and who survived past 1 year without recurrent malignancy were excluded from analyses of return to work because they did not report return to work information. The 146 patients who died or had recurrent malignancy before 1 year were scored as not returning to work. FIGURE 6 displays the cumulative incidence of return to full-time work, with competing risk of death or recurrent malignancy also indicated. Among patients with a history of work outside the home, 20% returned to full-time work by 1 year, 31% by 2 years, 33% by 3 years, and 34% by 5 years. Among 5-year survivors without recurrent malignancy and with a history of work or school outside the home before transplantation, 84% returned to full-time work or school. Return to work was significantly delayed for women (hazard ratio, 0.52; 95% confidence interval [CI], 0.33-0.82; $P=.005$). Patients with extensive chronic GVHD also had a nonsignificant trend toward delayed return to work (hazard ratio, 0.70; 95% CI, 0.4-1.1; $P=.10$). Cumulative incidence of return to work at 1 year for patients receiving autologous transplants was 23% and for allogeneic recipients it was 19%, a nonsignificant difference (hazard ratio over the first year, 0.57; 95% CI, 0.3-1.1; $P=.13$). The other medical, demographic, psychological, and physical risk factors tested with all outcomes did not predict return to work.

Table 3. Multivariate Model Predicting Depression Over Time (n = 252)*

Risk Factor	Coefficient (95% CI)†	*P* Value	*P* Value for Overall Test
Time (relative to pretransplantation baseline)			
90 Days	1.73 (0.70 to 2.76)	.001	<.001
1 Year	−1.00 (−2.57 to 0.57)	.21	
3 Years	−0.72 (−2.29 to 0.85)	.37	
5 Years	−2.15 (−3.63 to −0.67)	.004	
Female (vs male)	2.73 (1.46 to 4.01)		<.001
Extensive chronic GVHD	2.22 (0.47 to 3.97)		.01
History of chemotherapy before transplantation	−2.07 (−4.03 to −0.11)		.04
Pretransplantation social support, per point increase in support	−1.24 (−2.00 to −0.48)		.001
Pretransplantation physical limitations‡			
Pretransplantation	3.01 (1.46 to 4.56)	<.001	.002
90 Days	−3.84 (−5.72 to −1.96)	<.001	
1 Year	−2.35 (−4.80 to 0.10)	.12	
3 Years	−1.46 (−4.54 to 1.62)	.35	
5 Years	−3.41 (−7.73 to 0.92)	.06	
History of radiation therapy			
Pretransplantation	0.99 (−0.71 to 2.69)	.25	.001
90 Days	−2.19 (−4.06 to −0.32)	.02	
1 Year	−0.31 (−4.32 to 3.70)	.88	
3 Years	−1.15 (−3.89 to 1.58)	.41	
5 Years	4.84 (−0.84 to 10.52)	.09	

Abbreviations: CI, confidence interval; GVHD, graft-vs-host disease.
*Variables tested that did not predict depression included stem cell donor (autologous vs allogeneic), medical risk category, patient age, diagnosis, total body irradiation in conditioning regimen, education, marital status, and income. Because of its overriding correlation with depression ($r = 0.64$, $P<.001$), pretransplantation treatment-related distress was not entered into the final model.
†For risk factors with only main effects, the coefficient indicates mean difference from the reference group (eg, the reference group for female is male). For risk factors with interactions with time, the pretransplantation coefficient represents the difference between groups at pretransplantation. The 90-day to 5-year coefficients represent differences between groups in change from pretransplantation.
‡For physical limitations, the score is binary and yes indicates the score is >1 SD above age and sex-based population norms.

Full Recovery

To determine rates of full recovery, we evaluated the number of impairments reported at 1, 3, and 5 years. This analysis included physical and work limitations, depression, and distress. Among respondents at each time point, 19% (n=21) reported no impairments at 1 year, 49% (n=51) reported none at 3 years, and 63% (n=57) reported none at 5 years. At 5 years another 25% (n=23) had a single area of impairment, while 7% (n=6) had 2 areas of impairment.

COMMENT

Results of this prospective longitudinal study show that recovery after HCT occurs gradually over 1 to 5 years as measured by improvement in physical

function, return to work, depression, and treatment-related distress. Given adequate time, 84% of survivors returned to full-time work. At some point during treatment or recovery, 22% of the patients had symptoms consistent with clinical depression while an additional 31% had mild depressive symptoms. Higher levels of depression, lower levels of physical function, and less satisfaction with social support before HCT increased the risk of impaired physical and emotional recovery after the transplantation. Women had increased risk for depression, treatment-related distress, and delayed return to full-time work. Conversely, previous experience with chemotherapy or radiation therapy before beginning HCT seemed to facilitate recovery from the psychological aspects of this intensive treatment. Extensive chronic GVHD delayed recovery from depressive symptoms and marginally delayed return to work but did not significantly influence other outcomes. Although clinical impression suggests that autologous transplant patients recover more rapidly than allogeneic recipients, these groups differed only in more rapid recovery from treatment-related distress for autologous stem cell recipients.

Our results emphasize that recovery is not a unidirectional process of improvement. In general, physical recovery occurred earlier than emotional recovery. However, physical function remained susceptible to disruption by a variety of medical complications that can occur after the transplantation.[14,15,35] The proportion of participants with physical limitations increased from 12% at 1 year to 18% to 22% at 3 and 5 years, respectively. Similarly, emotional recovery fluctuated. Eight percent of patients who were not clinically depressed at 1 year were clinically depressed at 3 years. Although depression was not more prevalent in patients with physical problems at 1 year, at 3 and 5 years survivors with residual physical limitations were more likely to be depressed. Thus it seems that continuing physical complications began to take a toll on long-term survivors.

Both physical and psychological recovery progressed more slowly among participants with depression before HCT. In other studies, depression has been associated with increased mortality after the transplantation.[36] While our analyses did not examine the relationship between depression and mortal-

Table 4. Multivariate Model Predicting Distress Over Time (n = 234)*

Predictor	Coefficient (95% CI)†	*P* Value	*P* Value for Overall Test
Time (relative to pretransplantation baseline)			
90 Days	−0.35 (−0.63 to −0.08)	.01	<.001
1 Year	−0.66 (−0.96 to −0.36)	<.001	
3 Years	−0.80 (−1.21 to −0.39)	<.001	
5 Years	−0.80 (−1.05 to −0.54)	<.001	
Pretransplantation social support, per point increase in support	−0.12 (−0.19 to −0.05)		<.001
History of chemotherapy	−0.19 (−0.34 to −0.05)		.009
Diagnosis (relative to chronic leukemia)			
Lymphoma	0.00 (−0.19 to 0.20)	.96	.02
Acute leukemia	0.16 (0.04 to 0.29)	.01	
Allogeneic stem cell donor (relative to autologous)			
Pretransplantation	−0.10 (−0.29 to 0.10)	.34	.01
90 Days	0.24 (0.01 to 0.47)	.04	
1 Year	0.35 (0.11 to 0.59)	.005	
3 Years	0.35 (0.06 to 0.64)	.02	
5 Years	0.08 (−0.12 to 0.28)	.43	
Female			
Pretransplantation	0.35 (0.23 to 0.47)	<.001	.07
90 Days	−0.04 (−0.20 to 0.12)	.63	
1 Year	−0.09 (−0.30 to 0.12)	.42	
3 Years	−0.02 (−0.29 to 0.24)	.86	
5 Years	−0.20 (−0.36 to −0.05)	.01	
Physical limitations‡			
Pretransplantation	0.11 (−0.03 to 0.24)	.12	<.001
90 Days	−0.01 (−0.22 to 0.19)	.89	
1 Year	−0.03 (−0.29 to 0.23)	.82	
3 Years	0.13 (−0.14 to 0.40)	.33	
5 Years	−0.32 (−0.49 to −0.16)	<.001	
History of radiation therapy			
Pretransplantation	0.19 (−0.01 to 0.38)	.06	.005
90 Days	−0.02 (−0.26 to 0.23)	.88	
1 Year	−0.07 (−0.49 to 0.35)	.74	
3 Years	−0.46 (−0.73 to −0.20)	<.001	
5 Years	0.01 (−0.25 to 0.27)	.94	
Education, college degree or more			
Pretransplantation	0.01 (−0.11 to 0.14)	.84	.002
90 Days	0.18 (0.02 to 0.34)	.03	
1 Year	0.35 (0.13 to 0.56)	.002	
3 Years	0.05 (−0.25 to 0.34)	.75	
5 Years	−0.07 (−0.23 to 0.10)	.41	

Abbreviations: CI, confidence interval; GVHD, graft-vs-host disease.
*Variables tested that did not predict distress included stem cell donor (autologous vs allogeneic), medical risk category, chronic GVHD, patient age, total body irradiation in conditioning regimen, marital status, and income. Because of its overriding correlation with distress ($r = 0.64$, $P<.001$), pretransplantation depression was not entered into the final model.
†For risk factors with only main effects, the coefficient indicates mean difference from the reference group (eg, the reference group for female is male). For risk factors with interactions with time, the pretransplantation coefficient represents the difference between groups at pretransplantation. The 90-day to 5-year coefficients represent differences between groups in change from pretransplantation.
‡For physical limits, the score is binary and yes indicates the score is >1 SD above age and sex-based population norms.

ity, we found that moderate or severe depression and treatment-related distress adversely affected quality-of-life outcomes. Of note, depression and distress differed in both their trajectory of recovery and in risk factors, which emphasizes the value of separately evaluating these syndromes. Also important, the seeming advantages of lack of previous treatment and more education delayed recovery from treatment-related distress rather than being protective. Adequate management after a complex medical intervention such as HCT requires routine screening to detect depression or distress and allocation of resources for treatment. Cost-effective methods to achieve these aims are readily available.[37,38]

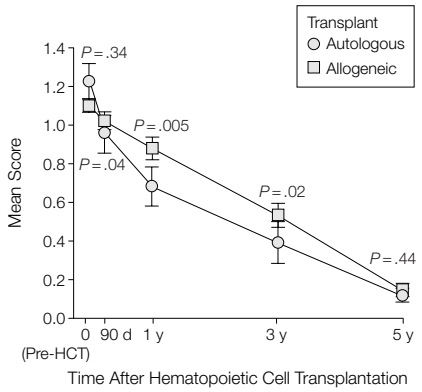
In a positive finding, medical risk factors that predict survival and short-term quality of life[19,20,24] did not have detectable influence on long-term outcomes among patients who survived. Among patients alive at 3 and 5 years, those who were older, those receiving allogeneic transplants or total body irradiation, and those with higher-risk diagnoses and disease stages had the same long-term quality of life as did patients with better medical prognoses. The exception, as hypothesized, was that the continuing presence of chronic GVHD increased the risk of long-term depression and was marginally associated with later return to work. Anecdotal reports from patients suggested that return to work was driven by financial needs or facilitated by flexibility in work responsibilities and did not necessarily indicate complete medical recovery.

Five-year survivors without recurrent malignancy did not differ from the entire cohort assessed in regard to physical limits or treatment-related distress after transplantation. Rates of clinical depression differed only at 1 year after HCT. These findings indicate that the changes described are not a result of more impaired patients dropping out of the longitudinal assessment as they died or their disease recurred. Rather, individual patients, whether long-term survivors or not, had similar patterns of change in physical limits, depression. and treatment-related distress.

As in all long-term follow-up studies, biases might have been introduced by missing data or unbalanced representation of the population. Groups that are underrepresented in our sample include autologous transplant recipients, patients who did not receive total body irradiation, and nonwhite or Hispanic transplant recipients. Our study did not include patients who were hospitalized soon after they arrived at the center. These patients were more likely to have high-risk characteristics and higher rates of mortality. However, the study did include an adequate representation of high-risk patients to permit statistical control for this factor. Our study also did not provide follow-up for individuals who had survived recurrent malignancy after the transplantation.

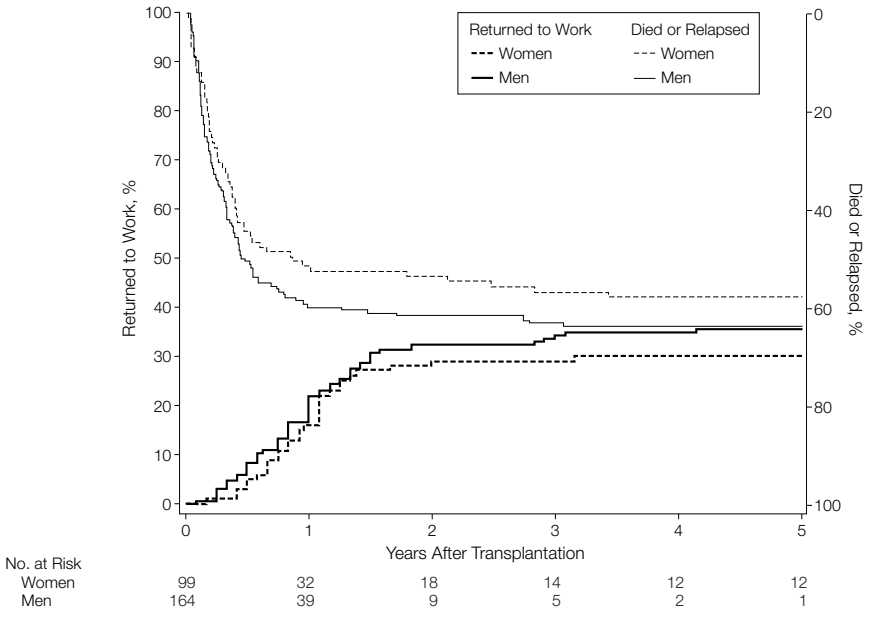
These results are both encouraging and cautionary. Patients, families, and medical teams depend on accurate recovery data when planning for post-transplant needs. Expectations that contradict actual experience cause stress for survivors and potential conflicts with family, work, and the medical team. To facilitate realistic planning, clinicians and patients should understand that full recovery requires more than a year for most survivors. Patients at risk for delayed recovery can be identified before transplantation. Rehabilitation programs, similar to those that have accelerated recovery for cardiac patients,[39]

Figure 5. Mean Scores for Treatment-Related Distress Comparing Autologous vs Allogeneic Transplant Recipients Over Time



Autologous recipients had more rapid decline in distress at 90 days, 1 year, and 3 years. Distress levels did not differ at pretransplantation or at 5 years. $P=.01$ for interaction of distress × time. HCT indicates hematopoeitic cell transplantation. Error bars indicate SEM.

Figure 6. Cumulative Incidence of Return to Full-time Work as a Function of Sex



might improve the physical and psychological health of HCT recipients and other patients who have survived after curative treatment for cancer.

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Study concept and design: Syrjala, Abrams, Martin.
Acquisition of data: Syrjala, Abrams, Sanders.
Analysis and interpretation of data: Syrjala, Langer, Abrams, Storer, Sanders, Flowers, Martin.
Drafting of the manuscript: Syrjala, Langer.
Critical revision of the manuscript for important intellectual content: Syrjala, Langer, Abrams, Storer, Sanders, Flowers, Martin.
Statistical expertise: Langer, Storer.
Obtained funding: Syrjala.
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Supervision: Syrjala, Abrams.
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