

ORIGINAL ARTICLE

Health-related quality of life in patients receiving reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation

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Reduced-intensity conditioning allogeneic HSCT (RIC) has less regimen-related morbidity and mortality than myeloablative allogeneic HSCT (MT) offering allogeneic transplantation to patients otherwise excluded. Whether these advantages improve health-related quality of life (HRQL) is unknown. We examined the HRQL effects of RIC and MT in patients with hematological diseases pre-transplant (baseline), days 0, 30, 100, 1 and 2 years following HSCT. HRQL was measured using the Short Form-36 Health Survey and the Functional Assessment of Cancer Therapy – General and BMT. Data were analyzed using mixed linear modeling adjusting for baseline HRQL differences. Patients (RIC = 41, MT = 35) were predominately male (67%), in remission/stable disease (65%) with an Eastern Cooperative Oncology Group status ≤ 1 (97%). HRQL progressively improved ($P < 0.01$) in both groups with higher scores at day 100 compared to days 0 and 30; there was no difference between groups during early recovery. At 2 years, all survivors ($n = 43$) reported HRQL similar or better than baseline. Results suggest RIC and MT patients experience a similar pattern of HRQL improvement during early recovery. Two-year survivors report a return to baseline or better in HRQL by day 100, with the exception of physical health in MT patients.

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Introduction

Myeloablative allogeneic HSCT (MT) is a potentially curative treatment for a variety of hematological diseases;

however, despite advances, transplant-related complications and transplant-related mortality remain high.¹ Consequently, application of MT has traditionally been limited to patients younger than 55 years of age with good performance status and no significant co-morbidities. Reduced-intensity conditioning allogeneic HSCT (RIC) evolved to decrease the regimen-related complications and mortality associated with MT. Many investigators now use RIC for patients otherwise precluded from MT, because the graft-versus-leukemia effects are retained despite potentially less cytoreduction of the disease burden by the conditioning regimen.²

Despite greater age and debility than the typical MT patient, patients undergoing RIC experience less mucositis, veno-occlusive disease, and neutropenic infection in the early post-transplant period.³ However, regimen-related complications within RIC regimens varies widely depending on the relative intensity of the conditioning.⁴

While there are numerous studies reporting clinical benefits following RIC, only one has addressed the impact of the transplant on the patient's perceived health-related quality of life (HRQL).⁵ Diez-Campelo *et al.*⁵ compared the HRQL in 47 patients undergoing RIC with 70 patients undergoing autologous HSCT. HRQL was measured with the Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) and eight additional investigator generated items across seven time points in the first year following HSCT (days 7, 14, 28, 90, 180, 270, 360). Repeated measures analysis revealed that the RIC group had significantly better physical function ($P = 0.049$) compared to the autologous group. Descriptively, the RIC group had better physical function at days 7, 14 and 28, suggesting that RIC spared patients from some of the functional limitations associated with the autologous HSCT. The two groups were similar at days 90 and 180. The autologous group reported better physical function at days 270 and 360. No significant differences between groups were found in the HRQL subscales of Functional Well-Being, Social/Family Well-Being or Emotional Well-Being.

Multiple studies have explored the effect of MT on HRQL^{6–30} with 13 comprehensive assessments of HRQL using standardized questionnaires.^{17–29} Two studies^{18,22}

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evaluated HRQL prospectively in an allogeneic sample using questionnaires with established reliability and validity. Of these, only one¹⁸ examined the early period post transplant (<day100) when the effects of a transplant conditioning regimen might be greatest. This study found that patients undergoing MT had an increase in overall dysfunction, especially with physical outcomes, compared to baseline. At 1 year, overall functional status was similar to baseline; however, physical function remained significantly impaired.

In this study, we prospectively examined HRQL in RIC and MT patients during the first 100 days following allogeneic HSCT to describe the trajectory of HRQL recovery. In addition, survivors were followed for 2 years to compare HRQL in these patients relative to baseline.

Patients and methods

Patients

A prospective survey of adult patients with hematological diseases undergoing allogeneic HSCT was conducted at the National Institutes of Health between October 1999 and September 2004. This study was approved by the National Heart, Lung and Blood Institute intramural Institutional Review Board and all patients provided written informed consent before participation. Of a total of 94 eligible patients literate in English or Spanish and receiving their first allogeneic transplant from an HLA-identical family donor, 78 (83%) agreed to participate in this HRQL study.

Patients received different conditioning regimens depending on the transplant research protocol. MT patients ($n = 36$) received cyclophosphamide 60 mg/kg once daily for 2 days (total dose = 120 mg/kg), fludarabine 25 mg/m² once daily for 5 days (total dose = 125 mg/m²) and fractionated total body irradiation ranging from 1200 to 1360 cGy with a T-cell-depleted peripheral blood stem cell (PBSC) transplant and low-dose cyclosporin A (CSA) as graft-versus-host disease (GVHD) prophylaxis. Patients undergoing the RIC protocols ($n = 42$) received an un-manipulated PBSC transplant and standard dose CSA as GVHD prophylaxis alone or in combination with MMF ($n = 7$). Twenty-three (55%) patients received cyclophosphamide 60 mg/kg once daily for 2 days (total dose = 120 mg/kg) and fludarabine 25 mg/m² once daily for 5 days (total dose = 125 mg/m²). Nineteen (45%) of the 42 patients received an RIC regimen that included pre-transplant immune depletion with EPOCH-F (etoposide 50 mg/m² as continuous infusion for 3 days (total dose = 150 mg/m²), prednisone 60 mg/m² once daily for 4 days (total dose = 240 mg/m²), vincristine 0.5 mg/m² as continuous infusion for 3 days (total dose 1.5 mg/m²), cyclophosphamide 600 mg/m², doxorubicin 10 mg/m² as continuous infusion for 3 days (30 mg/m²) and fludarabine 25 mg/m² once daily for 3 days (total dose 75 mg/m²), followed by the transplant conditioning regimen, including cyclophosphamide 1200 mg/m² once daily for 4 days (total dose = 4800 mg/m²) and fludarabine 25 mg/m² once daily for 4 days (total dose = 100 mg/m²).

Methods

Consecutive patients enrolled in allogeneic HSCT clinical research protocols were invited to participate in this study before receiving any transplant-specific chemo- or radiotherapy. Patients who agreed to participate were assessed for literacy in English or Spanish. After signing an informed consent document written in their primary language, patients completed questionnaires in their preferred language of English or Spanish using a touch screen notebook computer with specialized software (Assist Technology, Phoenix, AZ, USA). Patients completed HRQL questionnaires in a private room either on an inpatient transplant unit or in an outpatient clinic. If a patient was unable to return to the center at the 1- and 2-year follow-up, the questionnaires were mailed.

HRQL questionnaires (Functional Assessment of Cancer Therapy – General Version 4 (FACT-G), FACT-BMT³¹ and Short Form-36 Health Survey Version 1 (SF-36)³²), were completed at four time points to assess the trajectory of early recovery: (1) baseline (before any transplant-specific treatment) (FACT-G, SF-36); (2) the day of stem cell infusion (day 0) (FACT-BMT); and (3) within 1 week of days 30 and 100 following transplant (FACT-BMT, SF-36). In addition, post transplant data (FACT-BMT, SF-36) were collected at 1- and 2-year follow-up.

Questionnaires

The FACT-G is a 27-item cancer-specific questionnaire consisting of the following four subscales: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being and Functional Well-Being.³¹ The FACT-BMT adds a fifth subscale to the FACT-G, which assesses 'additional concerns' including overall treatment effects and 'regret' related to transplant.³¹ Higher total scores on the FACT-G (range 0–108) and FACT-BMT (range 0–148) indicate better HRQL. Normative data for the FACT-G are available from a general US adult population ($N = 1,075$; $M = 80.1$, $s.d. \pm 18.1$) within an age range from 18 to 91 years with 15% exceeding age 65. Both questionnaires have been shown to be reliable and valid measures in cancer patients.^{31,33–35} In this sample, the coefficient alpha reliability estimates³⁶ ranged from 0.88 to 0.90 (FACT-G) and 0.90–0.92 (FACT-BMT) over the first four time points.

The SF-36 is a 36-item, generic questionnaire that assesses functional status and well-being within eight multi-item subscales: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health.³² Using 1998 SF-36 norm-based scoring methods, subscales are aggregated to form two summary measures, the Physical Component Summary (PCS) and Mental Component Summary (MCS). Scores above 50 on these scales suggest physical and mental health higher than the average for the 1998 US general population (GP) ($N = 1982$; age $M = 50.7$, range 18–96).³² Age-adjusted norms from the 1998 GP were applied in this study. The psychometric properties of the SF-36 have been evaluated extensively.³² In this study, coefficient alpha reliability estimates³⁶ for the SF-36 PCS ranged from 0.90 to 0.92 and MCS ranged from 0.84 to 0.88 in the early transplant period.

Statistical analyses

Descriptive statistics were used to summarize: (1) demographic and clinical characteristics and (2) HRQL outcomes (FACT-BMT, SF-36 PCS and MCS), by transplant group, at baseline and 2-year survivor status. Baseline equivalence testing was performed by transplant group and survivor status on demographic characteristics (gender, age, marital status, education level, ethnicity), clinical status (disease, disease status and performance status) and baseline HRQL outcomes using Student's *t*-tests for continuous variables and χ^2 tests of independence for categorical variables. A Kaplan–Meier survival function was computed to present the survival pattern of the study sample by transplant group.

Three separate linear mixed model analyses were performed to test whether there were differences in HRQL outcomes within and between the RIC and MT groups over time. A group by time interaction term was also tested to explore whether any differences in the HRQL scores were a function of group, conditional on time. If this term was not significant, the main effects (treatment and time) were evaluated for significant differences.

In linear mixed modeling, a linear regression model is specified for each subject separately and multivariate linear models are used to relate the subject-specific regression parameters to subject characteristics (i.e. treatment). This method allows subjects to have their own time points of measurement with any pattern of missing data. All subjects with at least two time points beyond baseline were included. Each analysis first specified an unstructured or general within-subject variance–covariance matrix. These results were compared. There was no significant difference in fit; therefore, the more restrictive compound symmetry model was applied in this study after testing and meeting the homogeneity of variances and co-variances assumption.

Each model was adjusted using baseline HRQL scores (FACT-G, PCS, MCS) to statistically control for the predicted pre-transplant HRQL differences. Additional demographic and clinical variables were not adjusted in the final model to avoid removing the 'natural' composition of the groups. Eastern Cooperative Oncology Group (ECOG) status and age have been shown to be related to HRQL^{31,32} and therefore were considered to be partially controlled in each model. The sample size for this study was calculated to obtain sufficient power (80%) to detect a medium effect size (0.50) across time for each group. The alpha level was set at 0.05.

In addition to the primary analyses, *post hoc* exploratory analyses were performed to further evaluate the effect of RIC and MT on HRQL outcomes. If significant between- or within-group differences were observed for the composite indices, linear mixed modeling procedures were performed with each questionnaire subscale to identify the domain(s) of HRQL effected by treatment. In addition, paired and independent *t*-tests were used to test the significance of any change in HRQL observed between baseline and day 100, 1 and 2 years in the subgroup of survivors. *Post hoc* analyses were exploratory; therefore, no adjustments were made in the alpha level. Analyses were performed using the Statistical Package for the Social Sciences (SPSS®) version 13 software (SPSS Inc., Chicago, IL, USA).

Results

Patients

Figure 1 shows the study sample size and patient attrition over the study period. Of 94 eligible patients undergoing allogeneic HSCT, 78 (83%) agreed to participate in the HRQL study and completed baseline questionnaires. Before day 30, two (3%) patients declined to continue participation owing to language difficulties, and their data were excluded from the analyses. Therefore, 76 (81%) patients comprised the study sample for the day 100 analyses, with data from 43 survivors available for the 2-year exploratory analyses.

Baseline demographic and clinical characteristics of the RIC (*n* = 41) and MT (*n* = 35) patients are presented in Table 1. Patients who received RIC were approximately 11 years older than the MT patients (*P* < 0.001). The RIC and MT patients also differed in ethnicity (*P* < 0.001) and ECOG status (*P* = 0.001). A greater proportion of Caucasians were in the RIC group, whereas a greater proportion of Hispanics were in the MT group. ECOG status was worse in RIC patients compared to MT patients.

Seventy-two patients were evaluable for acute GVHD in the first 100 days following allogeneic HSCT. Seventeen (50%) of the MT patients experienced \geq grade 2 acute GVHD with a median onset of 40 days (range: 10–97). Seventeen (45%) of the RIC patients experienced \geq grade 2 acute GVHD with a median onset of 27 days (range: 10–98). Of the 58 (76%) patients evaluable for chronic GVHD, 14 (48%) patients in the MT group and 16 (55%) patients

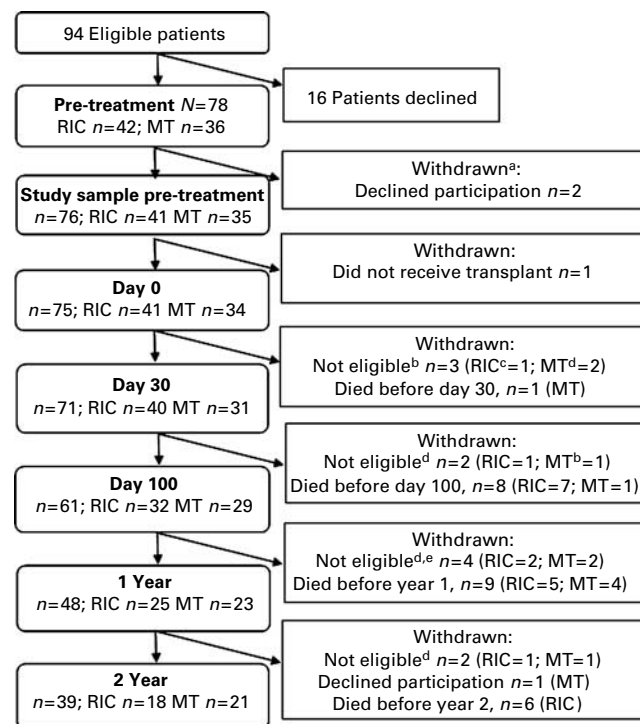


Figure 1 Study sample size and patient attrition over study period. ^aExcluded from analysis owing to concerns regarding ability to interpret questionnaires; ^bDied between days 30 and 100; ^cNew onset blindness; ^dRelapse requiring additional therapy; ^eDied between day 100 and 1 year.

Table 1 Baseline demographic and clinical characteristics, and HRQL outcomes scores for study sample by group

Characteristic	RIC (n=41), n (%)	MT (n=35), n (%)	P-value
Gender (male)	29 (71)	22 (63)	0.47
Age: mean \pm s.d.	45.4 \pm 14.5	34.1 \pm 9.1	<0.001
Married	27 (66)	21 (60)	0.45
<i>Education level</i>			0.12
High school or less	11 (27)	17 (49)	
Some college/trade	8 (19)	9 (26)	
College/post-graduate	22 (54)	9 (26)	
<i>Race/ethnicity</i>			<0.001
White/Caucasian	30 (73)	5 (14)	
Hispanic	6 (15)	17 (49)	
Black	3 (7)	2 (6)	
Asian	1 (2)	6 (17)	
Other	1 (2)	5 (14)	
Remission/stable	26 (63)	24 (69)	0.64
<i>Hematological disease</i>			—
Acute leukemia	—	13 (37)	
Chronic leukemia	11 (27)	18 (51)	
Lymphoma/MM	21 (51)	—	
MDS	6 (15)	3 (9)	
Non-hematological malignancy	3 (7)	0 (0)	
<i>ECOG status</i>			0.001
0	21 (51)	31 (89)	
1	19 (46)	3 (9)	
2	1 (2)	1 (3)	
<i>HRQL outcome</i>	<i>Mean \pm s.d.</i>	<i>Mean \pm s.d.</i>	<i>P-value</i>
FACT-G ^a	80.0 \pm 15.8	82.6 \pm 13.9	0.45
<i>SF-36^b</i>			
PCS	36.9 \pm 9.7	44.9 \pm 10.1	0.001
MCS	47.4 \pm 11.4	48.8 \pm 9.5	0.56

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FACT-G = Functional Assessment of Cancer Therapy – General; HRQL = health-related quality of life; MCS = Mental Component Summary Score; MDS = myelodysplastic syndrome; MM = multiple myeloma; MT = myeloablative HSCT; PCS = Physical Component Summary Score; s.d. = standard deviation; SF-36 = Short Form Health Survey – 36; RIC = reduced-intensity conditioning HSCT.

^aRange 0–108, higher scores equal better HRQL.

^b1998 US general population norm = 50, higher scores equal better HRQL.

in the RIC group experienced symptoms between day 100 and 2-year follow-up. The median onset for chronic GVHD in the MT group was 150 days (range: 100–473) and the RIC group was 151 days (range: 100–389).

Baseline demographic and clinical characteristics of the patients who survived through 2 years ($n=43$) and those who died ($n=32$) are presented in Table 2. Patients who died were approximately 9 years older than survivors ($P=0.003$). A greater proportion of patients dying in the first 2 years following transplant had progressive disease at the time of allogeneic HSCT ($P<0.001$) and an ECOG status of 1 ($P=0.002$) compared to survivors.

A Kaplan–Meier survival function for the sample is shown in Figure 2. For both groups, the greatest decline in survival occurred during the first 100 days following

transplant. A log rank (Mantel–Cox) test of equality of survival distributions for the two transplant groups from day 0 through 2 years was not significant ($P=0.109$). Of the 76 patients enrolled, four (5%) patients were not appropriate for inclusion in the survival function, three (4%) patients required a second allogeneic HSCT and one (1%) was not transplanted at the NIH. Of the 72 (95%) followed, 31 (43%) died during the 2-year follow-up, 20 (65%) from the RIC group and 11 (35%) from the MT group. The median survival for the RIC and MT groups was 564 and 730 days, respectively.

Health-related Quality of life

Cancer/treatment-specific HRQL (FACT-BMT). After adjusting for baseline FACT-G scores, there was no significant group by time interaction ($P=0.078$) and no significant difference in HRQL between treatment groups ($P=0.46$) (Figure 3a). There was a significant change ($P<0.001$) in HRQL over time in both groups with day 100 scores significantly higher than scores at days 0 and 30 ($P<0.001$). The mean increase in FACT-BMT scores for day 100 over day 0 (41 points) and day 30 (41 points) was consistent with a clinically important change in HRQL. *Post hoc* analyses showed improvements in the Physical Well-being ($P=0.001$), Functional Well-being ($P=0.001$), Emotional Well-being ($P=0.04$) and Bone Marrow Transplant concerns ($P=0.001$), with higher scores at day 100 compared with days 0 and 30. The Social/Family Well-being subscale did not meet the model assumptions and the analysis was un-interpretable.

There was no difference ($P=0.64$) between the baseline mean FACT-G score of patients who survived ($n=43$) and those who died ($n=32$) (Table 2). The HRQL effects in RIC patients who survived ($n=18$) showed a mean FACT-G score at day 100, 1 and 2 years similar to baseline ($P=0.24, 0.23, 0.53$, respectively) (Table 3). The mean FACT-G scores at day 100 and 1 year were approximately five points above the normative value for the general US adult population³⁷ and approximately six points higher than the norm at 2 years. In the MT patients who survived ($n=21$) the mean FACT-G scores at day 100, 1 and 2 years were also similar to baseline ($P=0.83, 0.38, 0.06$, respectively) (Table 3). The day 100 mean FACT-G score was not unlike the value for the general US adult population,³⁷ with scores above the norm at both the 1 (approximately four points) and 2 (eight points) year follow-up.

Physical health (SF-36 PCS). The baseline mean PCS score differed between groups ($P=0.001$) with the RIC patients showing poorer function. The RIC patients reported significantly lower scores in the Role-Physical, Physical Functioning and Pain subscales compared to the MT patients ($P=0.01, 0.003, 0.02$, respectively). After adjusting for baseline PCS scores, results indicated there were no significant group by time interaction ($P=0.62$) and no difference in PCS scores between groups ($P=0.97$) (Figure 3b). However, there was a significant difference in PCS scores across time ($P=0.008$), with scores at day 100 approximately three points higher than those at day 30,

Table 2 Baseline demographic and clinical characteristics, and HRQL outcomes scores for study sample by group and survival status

Characteristic	Survivors			Non-Survivors		
	Sample (n = 43), n (%)	RIC (n = 20), n (%)	MT (n = 23), n (%)	Sample (n = 32), n (%)	RIC (n = 21), n (%)	MT (n = 11), n (%)
Gender (male)	25 (58)	12 (60)	13 (57)	25 (78)	17 (81)	8 (73)
Age*: mean ± s.d.	36.2 ± 11.8	39.5 ± 14.4	33.3 ± 8.4	45.4 ± 14.1	51.0 ± 12.5	34.6 ± 10.6
Married	26 (61)	12 (60)	14 (61)	21 (66)	15 (71)	6 (55)
RIC	20 (47)	—	—	21 (66)	—	—
<i>Education level</i>						
High school or less	14 (33)	5 (25)	9 (39)	13 (41)	6 (29)	7 (64)
Some college/trade	13 (30)	6 (30)	7 (30)	4 (13)	2 (10)	2 (18)
College/post-graduate	16 (37)	9 (45)	7 (30)	15 (47)	13 (62)	2 (18)
<i>Race/ethnicity*</i>						
White/Caucasian	14 (32.6)	12 (60)	2 (9)	20 (63)	18 (86)	2 (18)
Hispanic	17 (40)	5 (25)	12 (52)	6 (19)	1 (5)	5 (45)
Black	2 (5)	1 (5)	1 (4)	3 (9)	2 (10)	1 (9)
Asian	6 (14)	1 (5)	5 (22)	1 (3)	0 (0)	1 (9)
Other	4 (9)	1 (5)	3 (13)	2 (6)	0 (0)	2 (18)
Remission/stable*	36 (84)	15 (75)	20 (87)	14 (44)	9 (43)	4 (36)
<i>Hematological disease</i>						
Acute leukemia	5 (12)	0 (0)	5 (22)	7 (22)	0 (0)	7 (64)
Chronic leukemia	21 (49)	6 (30)	15 (65)	8 (25)	5 (24)	3 (27)
Lymphoma/MM	10 (23)	9 (45)	1 (4)	12 (38)	12 (57)	0 (0)
MDS	4 (9)	2 (10)	2 (9)	5 (16)	4 (19)	1 (9)
Non-hematological malignancy	3 (7)	3 (15)	0 (0)	—	0 (0)	0 (0)
<i>ECOG status*</i>						
0	36 (84)	15 (75)	21 (91)	15 (47)	6 (29)	9 (82)
1	7 (16)	5 (25)	2 (9)	15 (47)	14 (67)	1 (9)
2	—	0 (0)	0 (0)	2 (6)	1 (5)	1 (9)
<i>HRQL outcome</i>						
	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.	Mean ± s.d.
FACT-G ^a	81.5 ± 13.6	82.3 ± 15.4	80.8 ± 12.2	79.9 ± 16.2	77.8 ± 16.2	83.9 ± 16.0
SF-36 ^b						
PCS*	42.7 ± 11.0	41.5 ± 9.2	48.8 ± 10.9	37.3 ± 9.2	36.9 ± 9.1	42.9 ± 7.0
MCS	47.6 ± 11.1	44.6 ± 12.7	47.6 ± 10.5	48.1 ± 9.8	47.8 ± 10.8	46.2 ± 8.5

Abbreviations: ECOG = Eastern Cooperative Oncology Group; FACT-G = Functional Assessment of Cancer Therapy – General; HRQL = health-related quality of life; MCS = Mental Component Summary Score; MDS = myelodysplastic syndrome; MM = multiple myeloma; MT = myeloablative HSCT; PCS = Physical Component Summary Score; s.d. = standard deviation; SF-36 = Short Form Health Survey – 36; RIC = reduced-intensity conditioning HSCT.

^aRange 0–108, higher scores equal better HRQL.

^b1998 US general population norm = 50, higher scores equal better HRQL.

* $P < 0.05$, survivor sample compared to non-survivor sample.

indicating an improvement in physical health. *Post hoc* analyses revealed improvements in the Physical Function subscale ($P = 0.001$) over time with higher scores at day 100 compared with day 30. No improvements were seen in the Bodily Pain ($P = 0.16$) or General Health ($P = 0.41$) subscales. The Role-Physical subscale did not meet the model assumptions and the analysis was un-interpretable.

The baseline mean PCS score of the patients who survived ($n = 43$) was significantly higher ($P = 0.027$) than those who died ($n = 32$) (Table 2). The PCS score of the RIC patients who survived ($n = 18$) at day 100, 1 and 2 years was similar to baseline ($P = 0.63, 0.34, 0.33$, respectively) (Table 3), with mean values consistently ≥ 0.5 s.d. below the age-adjusted GP norm.³² In the MT patients who survived ($n = 21$), the mean PCS score at day 100 was significantly below baseline ($P = 0.005$), with the

Role-Physical subscale significantly lower than the baseline value ($P = 0.02$) (Table 3). By 1 and 2 years, the mean PCS scores had improved; the 1-year score remained a 0.5 s.d. below the age-adjusted GP norm and the 2-year score was comparable to the age-adjusted GP norm.

Mental health. After adjusting for baseline MCS scores, there was no significant group by time interaction ($P = 0.30$) and no difference in MCS scores between groups ($P = 0.08$) (Figure 3c). There was a significant difference in MCS scores within group over time ($P < 0.001$). MCS scores at day 100 were approximately six points higher than day 30, indicating an improvement in mental health. *Post hoc* analyses revealed improvement in the Role-Emotional ($P = 0.001$), Social Functioning ($P < 0.001$), Vitality ($P < 0.001$) and Mental Health ($P = 0.025$)

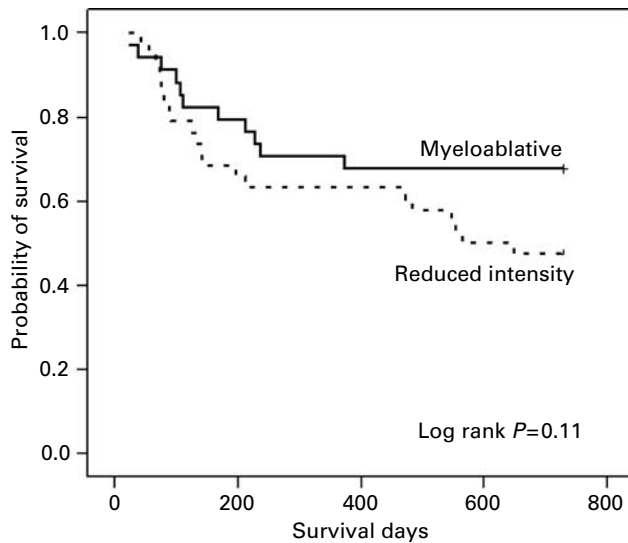


Figure 2 2-year Kaplan-Meier survival function of study sample ($N=72$).

subscales over time with higher scores at day 100 compared with day 30.

There was no difference ($P=0.85$) between the baseline MCS score of the patients who survived ($n=43$) and those who died ($n=32$) (Table 2). The RIC survivors ($n=18$) reported a mean MCS score significantly higher at day 100, 1 and 2 years compared to baseline ($P=0.03$, 0.01 , 0.02 , respectively) (Table 3). The mean MCS scores at day 100 and 1 year were comparable to the age-adjusted GP norm. At 2 years, the RIC patients' mean MCS score had improved and was comparable to a healthy age-adjusted subgroup in the GP. Significant improvements were observed in the Role-Emotional subscale scores at 1 ($P=0.009$) and 2 ($P=0.001$) years over baseline. In the MT patient survivors ($n=21$), mean MCS scores at day 100, 1 and 2 years were similar to baseline ($P=0.56$, 0.96 , 0.27 , respectively) and similar to the age-adjusted GP norm (Table 3).

Discussion

RIC allogeneic HSCT has quickly emerged as an accepted treatment for patients with potentially curable hematologic diseases, but with limiting co-morbidities. Although randomized clinical trials have not been conducted, it is generally accepted that RIC patients experience less morbidity^{3,4} and mortality^{4,38} compared to those undergoing MT, although one study reported similar survival rates.³⁹ Beyond these common biological outcomes, HRQL is increasingly being used to define the success of various therapies. Only one study has examined the HRQL of patients undergoing RIC, with results suggesting that this less intense therapy may protect patients from some of the difficulties with physical function known to accompany the more intense therapy (autologous) during the post transplant period.⁵ To our knowledge, no studies have examined

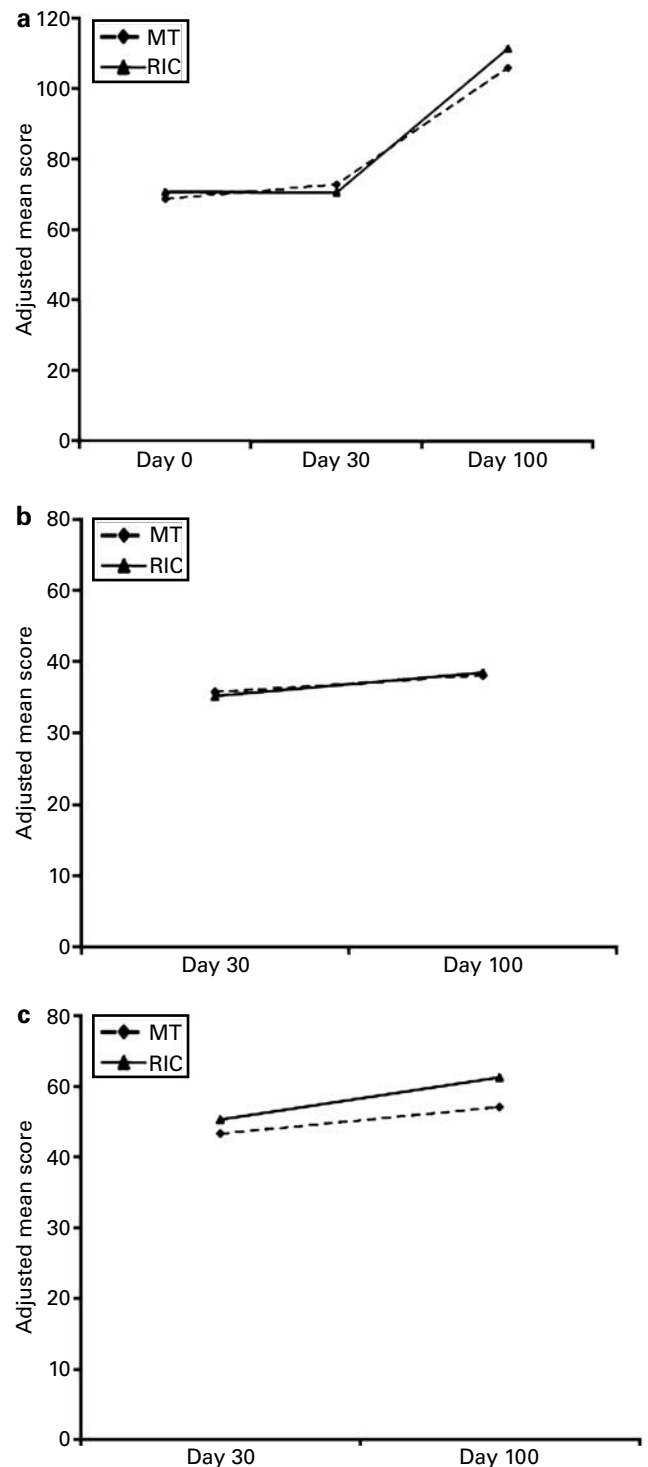


Figure 3 Adjusted mean scores over time by group for (a) Functional Assessment of Cancer Therapy - BMT (b) Short Form Health Survey - 36 Physical Component Summary (c) Short Form Health Survey - 36 Mental Component Summary.

the self-reported HRQL of patients undergoing RIC in context to another allogeneic population, MT patients.

Some common reasons patients with hematologic diseases qualify for RIC, as an alternative to MT, are

Table 3 SF-36 and FACT-G/BMT mean (\pm s.d.) scores for 2-year survivors ($n = 39^a$) by group and time

HRQL outcome	Group	Baseline	Day 0	Day 30	Day 100	1 year	2 year
<i>SF-36</i>							
PCS	RIC ^b	41.3 \pm 9.5	—	37.9 \pm 9.0	41.7 \pm 9.0	41.0 \pm 10.6	43.7 \pm 12.3
	MT ^c	48.4 \pm 11.3	—	38.1 \pm 6.9	42.0 \pm 8.5	47.4 \pm 10.2	49.1 \pm 9.2
MCS	RIC ^d	44.4 \pm 12.3	—	45.6 \pm 9.3	51.3 \pm 9.0	51.2 \pm 7.5	52.7 \pm 8.9
	MT ^e	47.4 \pm 10.9	—	41.0 \pm 8.7	46.2 \pm 10.6	48.1 \pm 12.0	50.6 \pm 7.6
<i>FACT</i>							
General ^f	RIC	82.4 \pm 16.2	70.6 \pm 13.0	74.2 \pm 17.6	84.9 \pm 15.1	84.8 \pm 13.5	85.7 \pm 16.0
	MT	81.2 \pm 12.7	67.8 \pm 15.1	70.8 \pm 11.1	80.5 \pm 14.2	83.9 \pm 14.6	88.4 \pm 12.4
BMT ^g	RIC	—	96.5 \pm 18.9	100.2 \pm 24.5	115.4 \pm 20.2	114.3 \pm 18.8	115.9 \pm 20.4
	MT	—	90.8 \pm 17.8	95.0 \pm 14.1	107.3 \pm 19.2	112.6 \pm 19.0	118.4 \pm 17.4

Abbreviations: BMT = bone marrow transplantation; FACT-G = Functional Assessment of Cancer Therapy – General; HRQL = health-related quality of life; MCS = Mental Component Summary Score; PCS = Physical Component Summary Score; SF-36 = Short Form Health Survey – 36.

^a $N = 43$; $n = 3$, off study; $n = 2$, alive, $n = 1$, mortality unknown; $n = 1$, declined 2-year survey completion.

^bAge-adjusted 1998 US GP norms (age range: 45–54 years) PCS mean 49.4 \pm 10.4.

^cAge-adjusted 1998 US GP norms (age range: 35–44 years) PCS mean 51.8 \pm 8.5.

^dAge-adjusted 1998 US GP norms (age range: 45–54 years) MCS mean 50.3 \pm 10.3.

^eAge-adjusted 1998 US GP norms (age range: 35–44 years) MCS mean 49.6 \pm 9.9.

^fRange 0–108, higher scores equal better HRQL; General US Adult Population Mean 80.1 \pm 18.1.

^gRange 0–148, higher scores equal better HRQL.

increased age, poor performance status and medical comorbidity. Consistent with this practice, the patients undergoing RIC in this study were older than those receiving MT, with poorer baseline performance status, evidenced in both ECOG and patient reported physical health (PCS). In the latter measure, the RIC patients reported more difficulty with pain and physical activities such as climbing stairs, walking and the ability to work. It is interesting to note that before treatment slightly more than one-third of the RIC patients reported being able to work ‘quite a bit’ or ‘very much’ as compared to over half of the MT patients.

Although empirical data indicate increased age and poor performance status negatively influence HRQL outcomes in patients undergoing allogeneic HSCT,^{7,22,35} it has been suggested that the RIC regimen might preserve HRQL in the older, more debilitated patient. In support of this prevailing perspective, the results of this study indicate that RIC patients have a steady pattern of improvement through day 100, which is similar to that reported by MT patients.

In both groups, improvements in HRQL are evident by day 100 across the various domains of HRQL, including physical, emotional, social and functional health. The timing and magnitude of these improvements coincide with dramatic improvements in the degree of concern associated with transplant-specific effects and are similar to results reported previously in mixed samples of MT and autologous patients.^{18,22} The first 100 days are a time when patients are commonly commuting to and from the transplant center for monitoring and toxicity management; acute GVHD being a toxicity of particular concern that can complicate a patient’s recovery. In this study, one-half of the RIC patients who had \geq grade 2 acute GVHD presented before day 30 (median 27 days), whereas those in the MT presented much later (median 40 days). The influence of acute GVHD on HRQL was not examined in this study and should be considered in future research. By

day 100, patients are commonly assuming more responsibility for their transplant recovery and preparing to reintegrate into their pre-transplant family, social and career roles.

Two-year survivors experienced an initial negative impact of treatment on HRQL, with one exception: there was a trend toward improvement in mental health in those receiving RIC. This increase in a feeling of well being may reflect a sense of ‘victory’ that can accompany the initial post transplant survival in these high-risk patients, despite ongoing limitations in their physical health status. By day 100, survivors in both groups had, on average, returned to their baseline HRQL. Exceptions include limitations in physical role function in those treated with MT and improvement in the mental health of patients who had received RIC, reaching levels higher than those observed at baseline. This improvement represents a clinically important change for the RIC patients who came to transplant with a mental health status well below an age-matched subgroup in the general population, and by day 100 were comparable.

By 2 years following allogeneic HSCT, patients in both groups had returned to baseline physical health. The 2-year physical health of the RIC survivors was an extension of a return to baseline by day 100, and, consistent with their pre-treatment health status, remained well below the age-adjusted GP norms. In fact, mean values were not unlike those for a 65 years and older subgroup. Ongoing problems included difficulties with work and other regular daily activities as a result of their physical health, and concerns about their general health, despite fewer cancer and transplant-related concerns. For the MT survivors, their 2-year recovery peak followed a pattern of gradual improvement in physical health corresponding with fewer cancer and transplant-related concerns. Although the recovery of physical health was slow, at 2 years the average physical health of the MT patients was comparable to the US GP of a similar age.

The 2-year evaluation of survivors also showed clinically important changes in the mental health of both groups, reaching levels above those observed at baseline. Patients in both groups experienced fewer role limitations resulting from emotional concerns, more satisfaction with their personal life and less fatigue. The results of this study are consistent with previous studies where patients reported a return to their baseline psychological health by 1 year.^{11,18} The improvements in mental health observed in the RIC group were particularly impressive, in general, and in light of their ongoing physical health challenges. These results occur early and are consistent with a sense of personal satisfaction or triumph at overcoming the odds often seen in these patients. Other studies have reported psychological growth following allogeneic HSCT in patients 3 or more years from transplant.^{24,40,41}

The major limitation of this study is related to the treatment group comparison. Patient assignment to treatment group was a clinical decision, rather than a random event. Although this design provides insight into the relative HRQL experiences of patients undergoing the two types of treatment as they unfold clinically, from patient selection through transplant, we are unable to conclude that the HRQL effects observed in this study could be attributed exclusively to the treatment itself, with randomization holding all other variables effectively constant. However, we elected to use baseline HRQL scores as covariates to statistically control for the initial differences between the groups and obtain a more precise estimate of treatment. In addition, the sample size for this study was predicated on a medium effect size difference across time in the HRQL of the groups with analysis of the difference between groups across time considered exploratory. Clearly, based on the results obtained, there was insufficient power (<15%) to detect a significant interaction effect. Although a much larger sample would provide 80% power to detect significant differences between groups across time, the difference would likely be small and not clinically meaningful.

The timing of HRQL questionnaire administration might also be considered a limitation of this study. Data were not collected between days 0 and 30. Therefore, the affect of the early reduction in morbidity associated specifically with the regimen might not have been captured in this study.

The evolution of RIC as an alternative for those previously ineligible for the more intense MT therapy has changed the face of treatment for patients with hematologic diseases. The reduction in immediate regimen-related toxicity has led to an assumption that RIC patients are protected from unbearable HRQL effects. Our results suggest that RIC patients, despite an initial decline in HRQL, report early HRQL recovery that persists up to 2 years following allogeneic HSCT. This conclusion provides additional context to counsel patients when considering RIC as a treatment option. The extent to which baseline factors are predictive of poor outcomes or enhanced probability of survival in RIC patient is unknown. This study highlights the value of quality of life studies to fully understand and more accurately define outcomes for this treatment approach.

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