Quality of Life Trajectories in Adolescent and Young Adult Versus Older Adult Allogeneic Hematopoietic Cell Transplantation Recipients.

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Abstract

Hematopoietic Cell Transplantation (HCT) is physically and psychologically challenging, potentially exposing patients to Quality of Life (QoL) impairments. Adolescent and Young Adults (AYAs aged 15-39) are a vulnerable cohort facing multiple hurdles due to dynamic changes in several aspects of their lives. The AYA population may be particularly prone to QoL issues during HCT. We hypothesized that due to the unique psychosocial challenges faced by AYAs, they would have an inferior quality of life. We studied QoL differences between AYA (15-39) and older adult (40-60) allogeneic HCT recipients before and after HCT. Additionally, we determined if pre-HCT QoL for AYA transplant recipients changed over time.

QoL data were collected prospectively before and after transplant on 431 recipients age 15-60 from June 2003 through Dec 2017 using the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT) questionnaire. Repeated measures analysis of variance was used to assess differences among age groups. Pearson correlation (r) was used to determine if
baseline QOL had improved after HCT from June, 2003 through December, 2017 in the AYA cohort.

QoL did not differ among younger AYA, older AYA, or older adults at any time in the first year after allogeneic HCT. At one year post-HCT, total FACT score and all FACT domains except physical well-being improved from pre-HCT, in all age groups. From 2003-2017, AYA allogeneic recipients experienced modest improvement in additional concerns ($r=0.26$, $p=0.003$), trial outcome index ($r=0.23$, $p=0.008$), and total FACT score ($r=0.19$, $p=0.031$), though no improvements were seen in physical, social, emotional, or functional well-being.

Contrary to our hypothesis, we found that QoL in the AYA population is similar to older adults before and after HCT. Improvements in QoL of AYA allogeneic patients since 2003 were driven by the additional concerns domain, which addresses multiple psychosocial aspects such as vocation, hobbies, and acceptance of illness. Continued efforts to tailor treatment and support for AYA HCT recipients is critical to improving QoL outcomes.

**Keywords**

AYA; QoL; HCT; FACT-BMT

**INTRODUCTION:**

The National Cancer Institute defines adolescent and young adult (AYA) patients as 15-39 years of age (1). Roughly 70,000 AYA patients are diagnosed with a malignancy each year which constitutes approximately 5% of all cancer diagnoses in the United States (2). Survival for AYA patients with cancer has lagged behind that of younger children (3, 4). This phenomenon may be explained by differences in host biology, impaired access to appropriate cancer treatment, and low participation in clinical trials. Additionally, AYAs are at a developmental stage marked by rapid changes in cognitive and emotional growth and AYAs historically experience a gap in services relating to their psychosocial needs (5, 6). Many of these factors place AYA patients at risk for poor quality of life (QoL) as they undergo treatment for cancer (7, 8).

Hematopoietic cell transplantation (HCT) is the only potentially curative option for many hematologic malignancies. AYA HCT patients have seen a consistent improvement in outcomes in recent years mirroring improvements seen in both children and older adult age groups (9–11). However, HCT is inherently an intensive process with many physical, social and psychological challenges. AYAs have longer life expectancy compared to older adults during which time QoL will be affected. From a psychosocial standpoint, AYAs may be more likely to deal with separation from peers, interruptions in education and inability to engage in or enjoy age appropriate activities. Moreover, they find themselves appropriately depending on their parents at a time they would otherwise be developing increased autonomy and struggling with the loss of control. Lahaye et al., found that long-term AYA survivors of HCT have ongoing physical and psychosocial consequences of past illness and its treatments when assessed at three years post HCT using the Schedule for the Evaluation of the Individual Quality of Life (Sei-QoL). Studies of children and adolescents using the
Child Behavior Checklist (CBCL) and Youth Self Report (YSR) questionnaires have also demonstrated impairments in the first years post-HCT(12). These survivors are at particular risk for psychosocial issues including affected self-image, social withdrawal, and a sense of lack of choice (13). AYA HCT recipients also have physical, psychological, social, and existential concerns including fear of the future and death and are at high risk to experience significant depression and anxiety(14). Interestingly, Pulewka et al., noted that AYA allogeneic HCT recipients had higher levels of physical and emotional functioning and similar perception of general health, mental health, and social role compared to older HCT patients, utilizing the FACT-BMT along with Human Activity Profile (HAP), Short Form Survey Instrument( SF-36), Life Orientation Test- Revised (LOT-R), and Berlin Social Support Scales (BSSS) questionnaire at D+100 and one year post HCT (15). Given the unique psychosocial issues faced by AYA HCT patients we hypothesized that QoL impairments may be more pronounced than in an older age group at baseline and in the first year post-transplant period and later on based on outcomes. We used baseline data as a covariate to illustrate any differences among the 3 cohorts going into HCT. Therefore, we compared whether the trajectory of QoL changes are different for AYAs when compared to an older adults.

METHODS

Patients

Using our institutional HCT program database, we identified consecutive patients with hematologic diseases age 15-60 years receiving their first allogeneic HCT with myeloablative conditioning for any diagnosis from June 2003 through December 2017. Patients were excluded if they did not consent for data to be used for research or if they had no pre-HCT QoL assessment. We anticipated many psychosocial aspects related to education, employment, and parental consent regarding decision making would be related to QoL among AYAs. We split the AYA cohort into two groups, younger AYAs (AYA 1; ages 15-29) and older AYAs (AYA 2; ages 30-39). This decision enabled equal distribution of patients in both groups. The age group that defines AYA population varies among different countries, and to an extent has been controversial, some experts suggest splitting the cohort them into early young adulthood (15-18 years), young adulthood (15-18 years), and late young adulthood(25-39 years)(16). Older adults were those 40-60 years of age; we excluded patients >60 years from analysis as this group has been previously compared to other adults (17). The study was approved by the Cleveland Clinic Institutional Review Board.

QoL Assessment

Functional Assessment of Cancer Therapy-Bone Marrow Transplant Scale (FACT-BMT) is a validated instrument for QoL evaluation(18). The FACT-BMT tool is a 50-item patient-reported questionnaire, which includes a 23-item BMT subscale. FACT-BMT measures four domains of well-being, physical (PWB), functional (FWB), social (SWB), emotional (EWB), and additional concerns (AC) which are specific to HCT. Two summary scores include the trial outcome index (TOI; PWB+FWB+AC); and total FACT-BMT score of all five domains. Higher scores correspond to better QoL. In our program, QoL using FACT-BMT is routinely administered by social workers within one month pre-HCT workup.
(baseline) and in follow up for the first year after HCT at days+100, +180, and +365. The questionnaires are in paper format and self-reported by the patients.

**Study Design and Statistical Methods**

This was a retrospective cohort study utilizing prospectively collected data to compare outcomes among AYA 1, AYA 2, and older adults. The primary outcome was QoL. Secondary outcomes included hospital length of stay, acute and chronic graft versus host disease (GvHD), relapse, non-relapse mortality (NRM), and overall survival (OS). Continuous variables were compared among AYA 1, AYA 2, and older adults using Kruskal-Wallis test and categorical variables were compared using Chi-square test. Repeated measures analysis of variance (RMANOVA) was used to assess differences among age groups and among time points; interaction between age group and time was assessed and was not significant for any QoL domain or score, and so only main effects were included. Missing QoL data was not imputed. Acute and chronic GVHD, relapse, and NRM were compared among groups with Gray test; OS was compared with log-rank test. Among all AYA patients, Pearson correlation (r) was used to determine if baseline QoL had improved during the course of the study. We categorized a correlation coefficient of .10 as a weak association, a correlation coefficient of .30 moderate, and .50 large (19). All p-values were two sided and p<0.05 was used to indicate statistical significance. Data were analyzed with SAS software®, version 9.4 (SAS Institute, Inc., Cary, NC).

**RESULTS**

**Patient Disease, Transplant Characteristics, and Outcomes**

Of 550 consecutive patients identified, 119 were excluded (116 were excluded did not have a pre-HCT QoL assessment and 3 were did not give consent for data use in research). Among 431 eligible patients, 76 were AYA 1, 60 were AYA 2, and 295 were older adults. Cohort characteristics are summarized in Table 1. Baseline differences were observed among age groups including race, performance status, disease risk classification, diagnosis, and HLA match. Platelet engraftment differed among groups, with the longest time to engraftment seen at a median of 27 days in AYA 2. Failure to complete the survey occurred at all time-points post-HCT, but was similar among age groups (Supplemental Table 1). No differences were found among age groups for length of stay, incidence of acute or chronic GVHD, incidence of relapse, NRM, or OS (Table 2).

**Quality of Life** The QoL trajectory was measured from baseline to one year post HCT. Total FACT-BMT scores were not different among age groups at any individual time points (p=0.83; Figure 1), nor were any of the FACT domains (0.39 ≤ p ≤0.82; Figure 2).

We also analyzed change in scores from baseline during the first year post-HCT in all age groups. PWB did not change within the first year of HCT (p=0.23) but all other FACT-BMT scores did change (p ≤0.005 for all, Figure 2). Specifically, SWB was lower at all follow-up times relative to baseline while EWB was higher at all follow-up times. FWB was lower at day +100, but then improved at days +180 and +365. AC and TOI only improved by day +365, and total FACT-BMT score improved at days +180 and +365.
Changes in AYA Baseline Quality of Life Since 2003

For AYAs, baseline QoL did not change from 2003-2017 for PWB (r=0.15, p=0.07), SWB (r=0.03, p=0.75), EWB (r=-0.06, p=0.47), or FWB (r=0.12, p=0.18). A modest improvement from 2003 to 2017 was seen in AC (r=0.26, p=0.003; Figure 3), which includes items related to physical appearance, finances, impact on relationships and familial concerns and this improvement in AC over time drove increases in TOI (r=0.23, p=0.008) and total score (r=0.19, p=0.031).

DISCUSSION

Adolescent and Young Adult allogeneic HCT recipients do not report inferior quality of life when compared to older adults, as demonstrated by multiple domains of FACT-BMT assessment in this study. This is particularly interesting as AYA patients face unique challenges during allogeneic HCT. Psychosocially AYAs in particular may face a major interruption in a stage of life where they are actively determining their education, career, finances and relationships. We hypothesized that these challenges unique to AYAs may lead to emotional and social isolation and subsequently affect their quality of life (5, 13, 14). It is possible that our study did not reflect a difference in QoL based on age group, due to the fact that physical and psychosocial hardships during HCT impact both AYA and older patients in a similar manner. Alternatively, the FACT-BMT QoL measurement tool used in this study may not have the granularity to identify the specific challenges unique to AYAs. For example, the FACT-BMT assessment did not ask specifically assess disrupted life plans, difficulty establishing romantic relationships, body image issues or limitation of leisure activities which all have significant impact on QoL. A QoL tool designed to more specifically address AYA concerns might have yielded different results (20).

Among AYAs, we observed a modest improvement in baseline additional concerns from 2003 to 2017 which drove improvements in the composite trial outcome index and total FACT score. However, we did not see any change over the same timespan for PWB, FWB, SWB, or EWB. In our center, the social work team performs a comprehensive assessment early before transplant to identify specific psychosocial needs. Patients are then provided with resources for additional psychological counselling if needed, and fertility preservation counseling, housing, and financial assistance as needed. Further, social workers conduct an assessment during every planned and unplanned inpatient admission. Additional concerns in FACT-BMT covers questions related to physical appearance, finances, and familial concerns and it is possible that our team has done a more thorough job assessing these matters in more recent years. However, the lack of improvement across other domains suggests that the addition of AYA centered cancer care to better target specific AYA concerns may be warranted (21).

Our study has several notable limitations. First, this was a single institution study and may not be generalizable, particularly with changes occurring over time since 2003. Our center’s focus on QoL overall, and AYAs in particular may not be generalizable as the QoL assessment tool that was used may have lacked the resolution to address AYA specific psychosocial concerns. Post-HCT attrition in our study could impact differences seen at multiple time-points during the study, and we did not perform imputation for missing data.
Patients with worse outcomes or more complications might have been less likely to complete the assessment at later time points, and we did not correlate specific complications post-transplant with QoL parameters (22). Our study also had comparable survival outcomes and Non relapse mortality between AYA and older adults which does not reflect the national SEER data. We did not adjust scores for baseline socioeconomic status, insurance status or other demographics which may affect outcomes. Additionally, the one year follow-up of these patients in our study does not address longer-term QoL in survivors. Finally, we did not compare the QoL of AYAs to children as QoL assessment tools for children are dissimilar to those of adults making conclusions challenging.

Overall, we found that AYAs had comparable QoL compared to older adults during the first year post-HCT period using a validated QoL tool specific to blood and marrow transplantation. Although it is unknown if the FACT-BMT assessment tool assess AYA specific needs as thoroughly as alternative methods, these data are encouraging for an otherwise vulnerable population. We also observed some evidence of improvement in QoL over time for AYAs. Although this modest improvement is promising, the lack of further improvement in other domains highlights the needs for dedicated AYA focused care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Highlights**

- AYAs had comparable QoL compared to older adults during the HCT period.
- AYAs have improved QoL over time, during transplant, since 2003
- Improvements in AYA QoL is driven by a domain that mainly addressed psychosocial concerns.
Figure 1:
Total FACT-BMT score by age group; Data shown as mean and standard error.
Figure 2:
FACT-BMT domain scores by age group. Data shown as mean and standard error.
Figure 3.
Change in Pre-HCT Additional Concerns from 2003-2017 in AYA 1 and AYA 2.


**Table 1:**

Patient, disease and transplant characteristics.

| Variable                        | AYA 1 (n=76) | AYA 2 (n=60) | Older Adults (n=295) | P-value |
|---------------------------------|--------------|--------------|---------------------|---------|
| **Age at Transplant**           |              |              |                     |         |
| median (range)                  | 25 (18-29)   | 34 (30-39)   | 51 (40-60)          | --      |
| **Sex**                         |              |              |                     |         |
| Male                            | 43 (65.5%)   | 43 (71.7%)   | 144 (48.8%)         |         |
| Female                          | 28 (34.5%)   | 17 (28.3%)   | 151 (51.2%)         |         |
| **Race**                        |              |              |                     |         |
| White                           | 65 (85.5%)   | 65 (79.2%)   | 274 (92.9%)         | <0.001  |
| Black                           | 6 (7.9%)     | 11 (14.5%)   | 16 (5.4%)           |         |
| Other                           | 5 (6.6%)     | 0 (0.0%)     | 5 (1.7%)            |         |
| **ECOG performance status**     |              |              |                     |         |
| 0                               | 44 (68.8%)   | 40 (66.7%)   | 130 (44.2%)         | 0.003   |
| 1                               | 18 (28.1%)   | 14 (23.3%)   | 123 (41.4%)         |         |
| 2                               | 2 (3.1%)     | 1 (1.6%)     | 14 (4.6%)           |         |
| **HCT-CI**                      |              |              |                     |         |
| Low                             | 28 (36.8%)   | 14 (23.3%)   | 85 (28.9%)          | 0.12    |
| Intermediate                    | 27 (35.5%)   | 26 (43.3%)   | 91 (31.0%)          |         |
| High                            | 21 (27.6%)   | 20 (33.3%)   | 118 (40.1%)         |         |
| **Number of prior chemotherapy regimens** | | | | |
| median (range)                  | 2 (0-7)      | 2 (0-5)      | 2 (0-9)             | 0.09    |
| **Prior radiation therapy**     |              |              |                     |         |
| Yes                             | 5 (6.6%)     | 5 (8.3%)     | 12 (4.1%)           | 0.32    |
| No                              | 71 (93.4%)   | 55 (91.7%)   | 283 (95.9%)         |         |
| **Months from diagnosis to transplant** | | | | |
| median (range)                  | 7.7 (1.2-114.3) | 5.7 (1.6-224.2) | 6.2 (0.3-329.1) | 0.69    |
| **Donor/recipient gender**      |              |              |                     |         |
| UCB to F                        | 2 (2.7%)     | 5 (8.3%)     | 17 (5.8%)           | 0.17    |
| UCB to M                        | 4 (5.4%)     | 5 (8.3%)     | 18 (6.2%)           |         |
| F to F                          | 17 (23.0%)   | 9 (15.3%)    | 50 (17.2%)          |         |
| F to M                          | 8 (10.8%)    | 5 (8.3%)     | 49 (16.8%)          |         |
| M to F                          | 13 (17.6%)   | 18 (30.5%)   | 81 (27.8%)          |         |
| M to M                          | 30 (40.5%)   | 17 (28.8%)   | 76 (26.1%)          |         |
| **HLA match**                   |              |              |                     |         |
| Matched                         | 51 (68.0%)   | 45 (75.0%)   | 239 (81.0%)         | 0.044   |
| Mismatched                      | 24 (32.0%)   | 15 (25.0%)   | 56 (19.0%)          |         |
| **Conditioning regimen**        |              |              |                     |         |
| Bu/Cy                           | 28 (36.8%)   | 23 (38.3%)   | 180 (58.1%)         |         |
| TBI/VP +/- ATG                  | 24 (32.0%)   | 15 (25.0%)   | 39 (13.1%)          |         |
| Flu/Cy/TBI                      | 2 (2.7%)     | 8 (13.3%)    | 26 (8.8%)           |         |
| Bu/Cy/VP                        | 4 (5.4%)     | 2 (3.3%)     | 15 (5.1%)           |         |
| Flu/TBI                         | 5 (6.6%)     | 4 (6.7%)     | 11 (3.7%)           |         |
| ECP/Cy/TBI                      | 7 (9.4%)     | 2 (3.3%)     | 7 (2.4%)            |         |
| TBI/VP/ATG                      | 5 (6.6%)     | 3 (5.0%)     | 12 (4.1%)           |         |
| Cy/ATG                          | 1 (1.3%)     | 3 (5.0%)     | 1 (0.3%)            |         |
| Other                           | - (-)        | - (-)        | 4 (1.4%)            |         |
| **Primary diagnosis**           |              |              |                     |         |
| Variable          | AYA 1 (n=76) | AYA 2 (n=60) | Older Adults (n=295) | P-value |
|-------------------|-------------|-------------|---------------------|---------|
|                   | N  | %  | N  | %  | N  | %  |                   |
| AML               | 28 | 36.8 | 31 | 51.7 | 126 | 42.7 | <0.001 |
| ALL               | 28 | 36.8 | 11 | 18.3 | 38  | 12.9 |
| MDS               | 8  | 10.5 | 4  | 6.7  | 56  | 19.0 |
| CML               | 7  | 9.2  | 6  | 10.0 | 30  | 10.2 |
| Lymphoma          | 2  | 2.6  | 1  | 1.7  | 18  | 6.1  |
| Other             | 3  | 3.9  | 7  | 11.7 | 27  | 9.2  |
| Donor type        |    |      |    |      |     |      |                   |
| Unrelated         | 38 | 50.0 | 31 | 51.7 | 115 | 39.0 | 0.08  |
| Related           | 27 | 35.5 | 15 | 25.0 | 132 | 44.7 |
| UCB               | 6  | 7.9  | 10 | 16.7 | 35  | 11.9 |
| Haplo             | 5  | 6.6  | 4  | 6.7  | 13  | 4.4  |
| GvHD prophylaxis regimen |   |      |    |      |     |      |                   |
| MMF-based         | 39 | 51.3 | 34 | 56.7 | 180 | 61.0 | 0.41  |
| MTX-based         | 35 | 46.1 | 26 | 43.3 | 109 | 36.9 |
| Other             | 2  | 2.6  | 0  | 0.0  | 6   | 2.0  |
Table 2:

Post Transplant outcomes;

| Outcome                  | AYA 1 | AYA 2 | Older Adults | P-value* |
|--------------------------|-------|-------|--------------|----------|
| **Length of stay, days** |       |       |              |          |
| median                   | 31    | 30    | 29           | 0.75     |
| range                    | 18-109| 17-111| 16-148       |          |
| **Grade II-IV Acute GVHD** |     |      |              |          |
| Day 100 estimate         | 43    | 35    | 35           | 0.38     |
| 95% CI                   | 32-54 | 23-47 | 30-40        |          |
| **Chronic GVHD**         |       |       |              |          |
| 1-year estimate          | 33    | 29    | 33           | 0.88     |
| 95% CI                   | 23-44 | 18-41 | 28-39        |          |
| **Relapse**              |       |       |              |          |
| 1-year estimate          | 24    | 20    | 21           | 0.41     |
| 95% CI                   | 15-34 | 11-31 | 17-26        |          |
| **Non-Relapse Mortality**|       |       |              |          |
| 1-year estimate          | 18    | 25    | 25           | 0.60     |
| 95% CI                   | 11-28 | 15-37 | 20-30        |          |
| **Overall Survival**     |       |       |              |          |
| 1-year estimate          | 67    | 63    | 62           | 0.76     |
| 95% CI                   | 55-76 | 50-74 | 56-67        |          |

p-values for GVHD, relapse, non-relapse mortality, and overall survival are based on the entire outcome curve using Gray or log-rank test.