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Adherence to Outpatient Oral Medication Regimens in Adolescent HSCT Recipients

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Abstract

Purpose—Hematopoietic stem cell transplantation (HSCT) is an increasingly utilized treatment option for adolescents with many life-threatening diagnoses. Suboptimal adherence may result in compromised treatment effectiveness and increased risk of adverse medical outcomes.

Method—This study examined adherence patterns in six adolescents (ages 12–18) who had undergone HSCT. Demographic and clinical information were obtained from caregivers and via chart review. Electronic pill bottles (Medical Event Monitors, MEMS™) were used to track medication adherence. Daily, weekly, and monthly adherence as well as medication interruptions (periods of 24 hours between doses) were calculated.

Results—Participants took 73% of doses (SD = 13%) and demonstrated perfect adherence on 56% of days (SD = 18%, Range = 34–88%). Average monthly adherence ranged from 40–91% and decreased over time. Participants demonstrated at least two [M(SD) = 4.20(2.28)] medication interruptions. Individual adherence patterns included high sustained adherence, variable adherence, and delayed non-adherence.

Conclusions—Overall, participants struggled to adhere to medication schedules, taking less than three-quarters of prescribed doses and demonstrating perfect adherence on fewer than four out of seven days per week. Adherence rates are similar to those observed in other pediatric populations and demonstrate the importance of routinely assessing adherence in adolescents who have undergone HSCT.

Keywords

Adolescent; Adherence; Hematopoietic stem cell transplantation

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Conflict of Interest Statement

None declared

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Driven by advances in research and clinical trials, hematopoietic stem cell transplantation (HSCT), a treatment once considered more beneficial for younger children, is now considered an effective treatment option for adolescents with oncological, hematological, and immunological diseases (Dini et al., 2011, Sava an and Abella, 2005). Between 2008 and 2010, approximately a third of pediatric HSCT recipients were between 10 and 19 years of age (National Marrow Donor Program, 2013). While survival rates for adolescents who have undergone HSCT have significantly improved, three year survival rates demonstrate wide variability and range from approximately 35–93% depending on the diagnosis (National Marrow Donor Program, 2012). In addition to numerous medical factors, adherence, or the “extent to which a person’s behavior (i.e., taking medications) coincides with medical or health advice”, is a modifiable factor that likely accounts for variation in these outcomes (Haynes, Taylor, & Sackett, 1979).

Following HSCT, adolescents and their caregivers must manage a complex treatment regimen. This regimen often includes the administration of numerous intravenous and/or oral medications with different dosing schedules and frequent dosing changes. In addition, adolescents and their caregivers are often asked to attend three to four clinic appointments each week and abide by activity restrictions (i.e., avoiding crowded places). As more complex medical regimens are associated with poorer adherence, individuals who must adhere to the post-HSCT regimen are at risk for non-adherence (Coleman et al., 2012).

Within this at-risk population, non-adherence may be particularly problematic for adolescents. Across numerous medical conditions, including many for which HSCT is the treatment of choice, adolescents demonstrate the highest rates of non-adherence (Butow et al., 2010, Pritchard et al., 2006). Rates of non-adherence among adolescents with cancer, for example, range from 27–63% (Butow et al., 2010). If rates of non adherence in adolescents who have undergone HSCT are similar to those demonstrated by other populations, a significant proportion of adolescents may be receiving sub-therapeutic doses of medication, compromising treatment effectiveness and placing them at increased risk for treatment failure and premature death (Pai and Drotar, 2010). Given these significant health implications and the modifiable nature of non-adherence, it is important to understand the prevalence of non-adherence in adolescent HSCT recipients.

The only investigation of adherence in HSCT recipients to date indicated that 40% of adolescents evidenced significant difficulty adhering to their oral antibiotic regimen during hospitalization (Phipps and DeCuir-Whalley, 1990). While qualitative findings suggest similar difficulties are present following discharge (Cooke et al., 2011), studies have not yet examined adherence during this difficult transition. Conceptualization of the post- HSCT regimen within the developmental framework of adolescence, however, suggests that adherence following discharge may be particularly problematic.

Following discharge, normative developmental goals of adolescence collide with the demands of the post-HSCT treatment regimen. Adolescents negotiate increasing independence and new social roles, resulting in unpredictable schedules, decreased parental supervision, increased parent-child conflict, and increased time away from home. In other adolescent chronic illness populations, these normative transitions increase the likelihood that adolescents will forget or choose to forgo treatment tasks (Butow et al., 2010, Pritchard et al., 2006). For example, it is normative for adolescents to place increased importance on peer relationships, making the social acceptance and enjoyment of engaging in social activities far more reinforcing than following a restrictive medical regimen.

Key barriers to adherence (i.e., conflict with caregivers, psychological disorders) also increase during adolescence (Kyngäs et al., 2000). The more barriers faced by adolescents

with a chronic condition, the higher the rates of non-adherence (Bregnballe et al., 2011, Gray et al., 2012). As a result of these risk factors, it is likely that rates of non-adherence in adolescent HSCT recipients following discharge may be even higher than the rate of 40% demonstrated during hospitalization (Phipps and DeCuir-Whalley, 1990).

Understanding medication non-adherence in this at-risk population is essential for determining methods to promote adherence to a daunting treatment regimen. The aims of this study were to be the first to describe individual and cohort-level patterns of oral medication adherence over a six- to nine-month period. We hypothesized that adherence would be similar to previously published oral medication adherence rates for adolescents with solid organ transplants or cancer (Butow et al., 2010, Dobbels et al., 2010).

Materials and Methods

Participants and Procedures

Data for this study are from a larger project examining adherence in pediatric HSCT recipients (Pai et al., 2011). Ninety-one of the 119 eligible participants agreed to participate (76% recruitment rate). The retention rate for the larger study was 99%.

The eight participants (ages 12–18 years) in the current study were recipients of a HSCT, prescribed oral medication, living with a caregiver, and fluent in English. Exclusion criteria included significant cognitive deficits (in the patient or both caregivers) and a medical status that precluded questionnaire completion.

Caregivers completed a questionnaire and were provided with an electronic pill bottle for use following discharge. Data were downloaded from pill bottles at four time points (1-, 3-, 6-, and 9-months). All procedures were approved by the Institutional Review Board and appropriate consent and assent were obtained.

Measures

Caregivers provided demographic information. Date of transplant, hospitalizations, and changes in medications were obtained via chart review. Immunosuppressant medication adherence was assessed using Medication Event Monitors (MEMS™), an electronic pill bottle that time-stamps each bottle opening. Participants were asked to use MEMS™ devices to store and administer their immunosuppressant medication for the nine-month study period. Medications stored in the MEMS bottles at baseline included: Cyclosporine (n = 3), Fluconazol (n = 1), Acyclovir (n = 1), and Voriconazole (n = 1). When immunosuppressant prescriptions were changed, participants were instructed to change the medications stored in the MEMS™ bottle. All participants evidenced at least one change in monitored immunosuppressant medication during the course of the study, and at study completion, medications in the MEMS™ bottles included: Acyclovir (n = 3), Prograf (n = 2), and Bactrim (n = 1).

Analyses

Two participants were excluded from analyses (loss of device, n = 1; discontinued use of device within 40 days, n = 1), resulting in a final sample of six participants. A-priori decision rules were applied to account for times when medications were not being dispensed from the bottle. Periods during which a patient was hospitalized, in the emergency room, or having a medication “held” by the medical team were coded as “non-monitored.” Data were also coded as “non-monitored” if families reported they were no longer using the MEMS™ bottle.

Daily adherence was calculated by dividing the number of pill bottle openings per day by the number of prescribed doses for that day. Weekly and monthly adherence values were calculated by computing the mean of daily adherence values across the specified time frame. The frequency and average length of medication interruptions (≥ 24 hours between doses) were calculated for all participants prescribed daily medication (n = 5).

Results

Participants were primarily male (67%), Caucasian (83%), and non-Hispanic (83%). On average, participants were 14.09 (SD = 1.67) years of age and 26.83 (SD = 10.93) days post-transplant at baseline. Medical diagnoses included: acute lymphoblastic leukemia (ALL, n = 2, 33%), Fanconi Anemia (n = 1, 17%), Medulloblastoma (n = 1, 17%), Hodgkin's Lymphoma (n = 1, 17%), and acute myeloid leukemia (AML, n = 1, 17%).

Adherence

Five participants (83%) reliably utilized MEMS™ for the duration of their immunosuppressant medication prescription (3 for 9 months, 1 for 4 months, and 1 for 7 months). Six months of data are also included for one patient who did not provide their MEMS bottle after the 6-month visit. Electronic monitor data were available for an average of 174.50 days per participant (SD = 67.19 days, Range = 110–268 days).

On average, participants took 73% of prescribed doses (SD = 13%, Range = 55–92%). Average number of doses taken per month ranged from 40% (SD = 26%) to 91% (SD = 13%) and decreased over time. Standard deviations (Range = 13%–33%) indicated that adherence varied widely across participants.

Mean percentage of days with perfect adherence (correct number of doses taken) was 56% (SD = 18%, Range = 34–88%). On average, participants failed to take all prescribed doses on 13% of days (SD = 14%, Range = 1–37%). All participants taking daily medication demonstrated at least 2 medication interruptions (periods of ≥ 24 hours between doses). On average, participants demonstrated 4.20 interruptions (SD = 2.28, Range = 2–7) lasting an average of 4.04 days each (SD = 4.60, Range = 1.5–12 days). Weekly adherence data for each participant are presented in Figure 1.

Individual Adherence Patterns

Participant 1 (P1) was a 12 year-old boy prescribed once-a-day Fluconazol at discharge. For the first 8 months of the study, P1 demonstrated variable weekly adherence ranging from 50–100%. After 31 weeks, P1 demonstrated a significant decline in adherence, taking no doses for several weeks. Examination of the electronic medical record did not identify any potential contributing factors (i.e., hospitalizations, changes in medications).

Participant 2 (P2) was a 13 year-old female prescribed three-times-daily Acyclovir at discharge. Similar to P1, P2 demonstrated variable adherence during the first few months of the study, with weekly adherence percentages ranging from 25–95%. Following a hospitalization three months after study entry, P2 demonstrated poor weekly adherence (0–7%) for several weeks. After her medication was changed from a twice-daily dosing schedule to once-a-day, P2 demonstrated significant improvement in her immunosuppressant adherence, averaging 100% weekly adherence for the remainder of the study.

Participant 3 (P3) was a 13 year-old female originally prescribed twice-a-day Cyclosporine. For the first five months of the study, P3 demonstrated consistently high weekly adherence (75–100%). Directly following a change to 3 times daily Acyclovir at 21 weeks, P3 began to

demonstrate lower levels of adherence (38–76%) that persisted for the remainder of the study.

Participant 4 (P4) was a 16 year-old male originally prescribed twice-daily Cyclosporine. While he evidenced good adherence initially (weekly average > 80% for 8 weeks), over time, P4 demonstrated a steadily decreasing pattern of adherence. Of note, the decreases in P4's adherence did not appear to correspond to changes in his medication regimen or hospitalizations.

Participant 5 (P5) was a 16 year-old male prescribed twice-daily Cyclosporine. P5 demonstrated consistently high weekly adherence (85–100%) for the first 23 weeks of the study. After discontinuing Cyclosporine and beginning Acyclovir three times daily at week 24, P5 began to evidence declines in adherence (42–100%). Of note, P5 did not return to the higher levels of adherence he evidenced at the beginning of the study.

Participant 6 (P6) was a 13 year-old male prescribed twice-daily Voriconazole. P6 demonstrated fairly consistent patterns of weekly adherence (57–100%) throughout the duration of the study.

Discussion

Adolescent HSCT recipients in this study demonstrated considerable non-adherence, taking an average of 73% of prescribed doses. Substantial variability in adherence was present within and across adolescents. Patterns of adherence included high sustained adherence, variable adherence, and delayed non-adherence. Results of individual-level data suggest that changes in medication regimens may partially contribute to changes in adherence over time.

Despite the critical health status of these adolescents and the significant implications of non-adherence, adherence patterns were similar to those observed in other pediatric populations (Butow et al., 2010, Dobbels et al., 2010, Pritchard et al., 2006). This is contrary to the often-held notion that their significant medical history will motivate adolescents who receive HSCTs to be adherent.

Adolescents missed at least one dose of medication about three days a week. This high number of missed doses inevitably impacts medication exposure, compromises treatment effectiveness, and could potentially increase the risk of adverse medical outcomes. These findings are troubling since problematic adherence is associated with an increased likelihood of HSCT-related mortality among adults (Pereira et al., 2010). Adherence difficulties became even more pronounced over time, decreasing from 91% during the first month following discharge to less than 80% after 3 months and less than 60% after 6 months. Consistent with previous research (Modi et al., 2011), these declines highlight the difficulty of maintaining a complex medical regimen.

The high prevalence of non-adherence in this study supports detailed and objective assessment of medication-taking patterns. Clinicians may wish to consider electronic monitoring devices similar to those used in this study (Ingerski et al., 2011). In addition, the variability in adherence across participants suggests that patient-centered, individualized adherence-promotion efforts may be most effective. Some patients may require intensive intervention efforts prior to and directly following discharge, while positive reinforcement and screening may be more appropriate for others.

As with most nascent areas of research, the generalizability of this study is limited by its small sample size. However, as the larger study had a recruitment rate of 83%, the participants in this study represent a large majority of adolescent HSCT recipients at one

pediatric hospital. In addition, electronic monitors represent a proxy for medication taking and the actual ingestion of the medication was not confirmed. Third, patients were not prescribed identical immunosuppressant regimens, and these differences may have impacted adherence patterns. Finally, the correlational nature of the data limits our ability to draw causal inferences. Future studies should include larger samples, include additional measures of adherence and examine potential predictors of adherence using qualitative and quantitative methods. Ultimately, randomized controlled trials are needed to determine variables that lead to changes in adherence and health outcomes among adolescent HSCT recipients.

This study is the first to examine adherence in adolescent HSCT recipients. Adolescents in this sample demonstrated substantial non-adherence consistent with rates of other pediatric populations. Additional research assessing the generalizability of these findings and the predictors and outcomes of non-adherence is needed. If replicated, these findings support the development of methods to assess and promote adherence and, ultimately, health outcomes of these courageous patients.

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Figure 1.
Weekly Percentage of Doses Taken for Each Participant
Note. Dashed line represents discontinuation of all oral medications.

Table 1

Demographic and clinical characteristics.

	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6
Adolescent						
Gender	Male	Female	Female	Male	Male	Male
Age at Transplant, yrs	12	13	13	16	16	13
Diagnosis	Supratentorial primitive neuroectodermal tumors	Acute Lymphoblastic Leukemia	Fanconi Anemia	Pre-B Cell Acute Lymphoblastic Leukemia	X-linked Lymphoproliferative Disease	Acute Myeloid Leukemia
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
Ethnicity	Non-Hispanic	Non-Hispanic	Hispanic	Non-Hispanic	Non-Hispanic	Non-Hispanic
Caregivers						
Primary Caregiver	Mother	Mother	Mother	Mother	Mother	Mother
Marital Status	Married	Married	Married	Married	Married	Married
Family						
Income	> \$100,000	--*	\$20,000 - \$29,999	> \$100,000	\$40,000 - \$49,999	> \$100,000
Household Size	6	4	3	4	4	5

Note.

* Participant 2 chose not to answer this question

Table 2

Adherence variables for each participant.

	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6
Medication monitored	Fluconazol	Acylovir	Cyclosporine	Cyclosporine	Cyclosporine	Voriconazole
Changes in medication, N	1	3	1	1	1	1
Adherence, M (SD)	66.33 (35.86)	58.44 (41.83)	78.37 (20.19)	67.96 (21.47)	83.56 (20.73)	92.33 (11.80)
Days with Correct Doses, N (%)	N/A *	61 (47%)	126 (52%)	60 (34%)	161 (60%)	97 (88%)
Days with No Doses, N (%)	N/A	49 (38%)	13 (5%)	16 (9%)	3 (1%)	4 (4%)
Medication Interruptions, N	N/A	3	6	7	2	2
Medication Interruptions, M (SD) days	N/A	12.25 (15.97)	1.2 (2.40)	2.29 (2.56)	1.50 (0.71)	2.00 (0.00)

Note.

* Daily data not calculated for patient 1 as no daily medications were prescribed.