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Comparison of self-report and electronic monitoring of 6MP intake in childhood ALL: A Children's Oncology Group study

Wendy Landier, PhD, RN,[1] Yanjun Chen, MS,[1] Lindsey Hageman, MPH,[1] Heeyoung Kim, MPH,[2] Bruce C Bostrom, MD,[3] Jacqueline N Casillas, MD, MSHS,[4] David S Dickens, MD,[5] William E Evans, PharmD,[6] Kelly W Maloney, MD,[7] Leo Mascarenhas, MD, MS,[8] A Kim Ritchey, MD,[9] Amanda M Termuhlen, MD,[8] William L Carroll, MD,[10] Mary V Relling, PharmD,[6] F Lennie Wong, PhD,[2] Smita Bhatia, MD, MPH[1]

[1]University of Alabama at Birmingham, AL; [2]City of Hope, Duarte, CA; [3]Children's Hospitals and Clinics of Minnesota, Minneapolis, MN; [4]David Geffen School of Medicine at UCLA, Los Angeles, CA; [5]Helen DeVos Children's Hospital at Spectrum Health/Spectrum Health at Butterworth Campus, Grand Rapids, MI; [6]St. Jude Children's Research Hospital, Memphis, TN; [7]University of Colorado School of Medicine, Aurora, CO; [8]Children's Hospital Los Angeles, CA; [9]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; [10]Perlmutter Cancer Center, NYU-Langone Medical Center, New York, NY

Correspondence: S. Bhatia, MD, MPH, Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, 1600 7th Avenue S, Birmingham, AL 35233; Telephone: (205) 638-2120; Fax: (205) 638-2121; sbhatia@peds.uab.edu

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KEY POINTS

- Self-report over-estimated electronically monitored 6MP adherence at least some of the time in the large majority (84.4%) of patients.

- Non-adherers were more likely to over-report 6MP intake (47%) compared with adherent patients (8%).

ABSTRACT

Adequate exposure to oral 6-mercaptopurine (6MP) during maintenance therapy for childhood acute lymphoblastic leukemia (ALL) is critical for sustaining durable remissions; the accuracy of self-reported 6MP intake is unknown. We aimed to directly compare self-report to electronic monitoring (Medication Event Monitoring System [MEMS]), and identify predictors of over-reporting in a cohort of 416 children with ALL in first remission over 4 study months per patient (1,344 patient-months for the cohort) during maintenance therapy. Patients were classified as "perfect reporters" (self-report=MEMS), "over reporters" (self-report>MEMS by ≥5 days/month for ≥50% of study months), and "others" (all patients not meeting criteria for perfect- or over-reporter). Multivariable logistic regression examined sociodemographic and clinical characteristics, 6MP dose-intensity, *TPMT* genotype, TGN levels, and 6MP non-adherence (MEMs-based adherence rate <95%) associated with the over-reporter phenotype; generalized estimating equations (GEE) compared 6MP intake by self-report and MEMS over the study period. Self-reported 6MP intake exceeded MEMS at least some of the time in 84% of patients. Fifty (12%) patients were classified as perfect reporters, 98 (23.6%) as over-reporters, 2 (0.5%) as under-reporters, and 266 (63.9%) as others. Multivariable logistic regression technique identified the following variables associated with the over-reporter phenotype: i) non-white race: Hispanic, odds ratio (OR)=2.4, 95%CI, 1.1-5.1, p=0.02; Asian, OR=3.1, 95%CI, 1.2-8.3, p=0.02; African-American, OR=5.4, 95%CI, 2.3-12.8, p=0.0001; ii) paternal education <college (OR=1.4, 95%CI, 1.0-2.0, p=0.05); and iii) 6MP non-adherence (OR=9.4, 95%CI, 5.1-17.5, p<0.0001). Self-report of 6MP intake in childhood ALL over-estimates true intake, particularly in non-adherent patients, and should be used with caution.

INTRODUCTION

Children with acute lymphoblastic leukemia (ALL) require adequate exposure to oral 6-mercaptopurine (6MP) during the maintenance phase of therapy in order to sustain durable remissions.[1] Prior studies of adherence to oral 6-MP in children with ALL have reported adherence rates ranging from 70% to 95%, using a variety of subjective and objective measures.[2-9] We have previously shown that inadequate systemic exposure to 6MP due to poor 6MP adherence (<95% adherence rate, objectively measured by the Medication Event Monitoring System [MEMS; WestRock Healthcare, Sion, Switzerland]), is associated with increased risk of relapse.[2,10] Accurate assessment of 6MP intake is therefore critical to ensure timely interventions for patients with poor adherence.

Self-report is a convenient and inexpensive method to monitor 6MP intake in the clinic; however, literature in the non-oncology setting indicates that self-report is subject to over-reporting.[11-14] The accuracy of self-reported 6MP intake during maintenance therapy for childhood ALL is not known. In this study, we address this issue by directly comparing self-report to electronic monitoring of 6MP intake, and identifying predictors of over-reporting of 6MP intake in a racially and geographically diverse cohort of children with ALL during the maintenance phase of therapy.

METHODS

Study Participants

Participants were enrolled on the Children's Oncology Group (COG) study AALL03N1 (NCT00268528) by 87 participating institutions (Supplemental Materials, Table S1, online only) after obtaining approval for the study from local institutional review boards. Written informed consent/assent was obtained from all patients and/or parents/legal guardians; patients and their parents/caregivers did not receive incentives for study participation. Eligibility criteria included a

diagnosis of ALL at age 21 years or younger; in first remission; belonging to one of four self-reported racial/ethnic groups (Asian, African American, Hispanic and non-Hispanic white); and receiving maintenance chemotherapy that included self- or parent/caregiver-administered oral 6MP. Although the participation rate of study participants across the 87 participating institutions is not available, we have previously shown that the AALL03N1 study participants were comparable to patients enrolled on the relevant parent COG therapeutic frontline ALL protocols.[15] Only patients who had both evaluable MEMS and self-report data were included in this analysis.

Self/Parent Report

Self-report of 6MP intake was assessed at 4 study time points (Day 29 = study month 1, Day 57 = study month 2, Day 113= study month 4, and Day 141 = study month 5; see study schema, Figure 1) using a questionnaire that elicited the number of days that 6MP was taken over the past 4 weeks, i.e., "During the past 28 days (4 weeks), how many days did you [your child] take 6MP? (Please fill in the blank): I [My child] took 6MP on ___days out of the past 28 days." For the patients where the reported number of days of 6MP intake was less than 28, the questionnaire did not elicit the number of days that 6MP was held for physician-directed holds vs. patient/parent-directed reasons. Thus, the self-report questionnaire assessed the number of days of 6MP intake (irrespective of reasons for 6MP holds if any), rather than adherence to the prescribed regimen. The questionnaire was available in English, Spanish, and several Asian languages, and was completed by parents of patients younger than 12 years of age; by both parents and patients, for patients between the ages of 12 and 17 years; and by patients 18 years of age or older at study participation.

Electronic Monitoring

6MP intake (irrespective of reasons for 6MP holds if any) was monitored electronically by placing a MEMS™TrackCap® on the patient's 6MP bottle. The MEMS™TrackCap® uses

microelectronic technology to record the date/time of each bottle opening for the study duration (Figure 2). Patients/parents were informed about the purpose of MEMS-based assessment, and were instructed to take all 6MP doses from the MEMS bottle throughout the study period. At the end of the study period, the MEMS data were downloaded (Figure 3).

Demographic Questionnaire

Patients (18 years of age or older at study) or parents (of patients <18 years of age at study) completed a demographic questionnaire at study entry, providing information regarding patient race/ethnicity, parental education, and annual household income.

Healthcare Provider Reports

Monthly reports were completed by participating institutions for each patient, detailing the prescribed 6MP dose for each day of the preceding month, and any dates when 6MP was held for toxicity or illness. This information was used to calculate 6MP dose-intensity and the MEMS-based adherence rate for each patient. 6MP dose-intensity was defined as the ratio of the 6MP dose *actually* prescribed, to the planned protocol dose (75mg/m^2/day). The MEMS-based adherence rate was calculated as the ratio of the number of days with MEMS cap openings (X) to the number of days 6MP was prescribed (N), reported as a percentage (X/N*100); days when 6MP was withheld by the prescriber were removed from the denominator (N).

Statistical Analyses

Self-report vs. electronic monitoring of 6MP intake: The electronic (MEMS) record of 6MP intake was compared with the self-report record for each of the 4 study months that elicited self-reported 6MP intake. For patients age 12-17 years, from whom both patient- and parent-reported 6MP intake were collected, only patient report was used in the analysis, as the patient-parent reporting were found to be highly correlated (Supplemental Materials, Table S2, online

only). Correlation between electronically monitored and self-reported days of 6MP intake was assessed using the Pearson correlation coefficient[16] and interpreted by Cohen's convention.[17]

Mean days of 6MP intake (by self-report and electronic monitoring) over the study period were compared using generalized estimating equation (GEE) analysis,[18] adjusted for covariates. The covariates considered included sex, race/ethnicity, age at study entry, annual household income, maternal and paternal education, National Cancer Institute (NCI) risk group,[19] 6MP dose-intensity, red cell thioguanine nucleotide (TGN) levels,[20] and thiopurine methyltransferase (*TPMT*) genotype.[21] Backward step-wise procedure was used to eliminate non-significant variables until a parsimonious model consisting of variables with $p<0.1$ was obtained.

Patterns of self-report vs. electronic monitoring of 6MP intake: Patients were classified as 'perfect reporters' if their self-report matched their electronic records for each study month; 'over-reporters' if their self-reported days of 6MP intake exceeded their electronic record by 5 or more days for at least half of the study months; 'under-reporters' if the number of days of self-reported 6MP intake was less than their electronic record in all study months; the remainder of the cohort was classified as 'others.'

Predictors of the over-reporter phenotype: Multivariable logistic regression analysis was used to identify predictors of the over-reporter phenotype. The following variables were examined univariately, and were included in the multivariable model if their univariate *P*-value was <0.1: age at study entry, sex, race/ethnicity, annual household income, maternal and paternal education, NCI risk classification, 6MP dose-intensity, red cell TGN levels, and 6MP non-adherence (MEMS-based adherence rate <95%)[2]. *TPMT* genotype was retained in the model regardless of *P*-value, to account for frequent dosing fluctuations that may occur in non-wild type patients.

Sensitivity and specificity of self-reported 6MP intake: MEMS-based 6MP intake was considered the 'gold standard' (i.e., indicator of true 6MP intake). Using electronically monitored 6MP intake records, patients were dichotomized into those with 6MP bottle openings on <95%

of study days and those with 6MP bottle openings on ≥95% of study days (based on our previously-reported findings that 6MP adherence rates <95% were associated with a significantly increased risk of relapse).[2] The sensitivity of self-report in detecting true (i.e., MEMS-based) 6MP intake <95% was defined as the proportion of patients with self-report <95% among the patients with MEMS-report <95%. The specificity of self-report was defined as the proportion of patients with self-report ≥95% among the patients with MEMS-report ≥95%.

PROCs CORR, GENMOD, LOGISTIC of SAS software, version 9.4 (SAS Institute, Cary, NC) were used for analysis. Two-sided tests with *P* <0.05 were considered statistically significant.

RESULTS

Patient characteristics

The cohort consisted of 416 patients who contributed a total of 1,344 patient-months of self-report and MEMS data for this study, collected over 4 study months per patient. Of the 416 study participants, 412 completed the study (99% retention rate). The clinical and sociodemographic characteristics of the cohort are summarized in Table 1. Median age at study participation was 6.0 (range, 2-20) years; 66.6% were male; 35.6% were non-Hispanic white, 37.0% Hispanic, 13.5% Asian and 13.9% African American; 38.4% had high-risk disease by NCI criteria.

Self-report vs. electronic monitoring of 6MP intake

Overall, the cohort members self-reported taking 6MP for 92.6% of the total days of observation, while the MEMS cap records indicated 6MP bottle openings on 83.7% of the days. Correlation between the mean number of days of 6MP intake by self-report and electronic monitoring by study month was moderate (r = 0.36 [95% confidence interval (CI) 0.27-0.45] P<0.0001 to r = 0.58 [95%CI 0.50-0.66] P<0.0001). GEE estimates of adjusted mean days per

month of 6MP intake for the 4 study months by self-report vs. electronic monitoring were 25.8±5.4 to 26.3±3.7 vs. 22.8±6.6 to 25.3±4.4, respectively (P<0.0001; Figure 4).

Comparing self-report to electronic monitoring for each patient, we found that 12.0% (50/416) of the patients were perfect reporters (self-report = MEMS across all study months); 23.6% (98/416) of the patients were over-reporters (self-report exceeded electronic monitoring by 5 or more days for half or more of the study months); 0.5% of the patients (2/416) were under-reporters (self-report <MEMS across all study months), and the remaining 63.9% (266/416) of the patients were placed in the "other" category. For 95.1% (253/266) of the patients classified as "other," self-reported 6MP intake exceeded electronic monitoring by one or more days in one or more study months. Thus, for 84.4% (351/416) of the entire cohort, self-report of 6MP intake exceeded the MEMS report at least some of the time.

Predictors of the over-reporter phenotype

Multivariable logistic regression modeling (adjusted for age at study entry, annual household income, NCI risk classification, 6MP dose intensity, and *TPMT* genotype) identified the following predictors of the over-reporter phenotype (comparison group: all others): i) non-white race: Hispanic, OR=2.4, 95%CI, 1.1-5.1, p=0.02; Asian, OR=3.1, 95%CI, 1.2-8.3, p=0.02; African-American, OR=5.4, 95%CI, 2.3-12.8, p=0.0001 (referent group: non-Hispanic whites); ii) paternal education <college: OR=1.4, 95%CI, 1.0-2.0, p=0.05 (referent group: paternal education: ≥college degree); and iii) 6MP non-adherence: OR=9.4, 95%CI, 5.1-17.5, p<0.0001 (referent group: 6MP adherers) (Table 2). While 77/98 (78.6%) of the *over-reporters* had MEMS-based adherence rates <95% (non-adherers), none of the *perfect reporters* were non-adherers (p<0.001). In the subset of 77 non-adherent patients who were over-reporters, there was a negative correlation between mean adherence rate and number of days of over-reporting (r= -0.81, p<0.0001).

GEE estimates of adjusted mean days of 6MP intake over the four study months by self-report vs. electronic monitoring for the cohort are shown in Figures 5a-c, with findings from the

analyses stratified by race/ethnicity (Hispanics, Asians, African Americans and non-Hispanic whites), by paternal education (<college degree and ≥college degree) and by adherence (non-adherers and adherers).

Sensitivity and specificity of self-reported 6MP intake

The sensitivity of self-report for detecting true (i.e., MEMS-based) 6MP intake <95% was 52.7% (95% exact binomial CI: 46.8%-58.5%). The specificity of self-report for detecting MEMS-based intake ≥95% was 95.8% (95% exact binomial CI: 90.5%-98.6%). When the cohort was stratified by adherence status, sensitivity of self-report for detecting true 6MP intake was 61.8% among adherers and 45.4% among non-adherers.

DISCUSSION

To our knowledge, this is the first study to directly compare self-report of 6MP intake with electronic monitoring in children with ALL during the maintenance phase of therapy. In this multiracial Children's Oncology Group cohort drawn from 87 geographically-diverse institutions, we found that over-reporting of 6MP intake is common. The large majority (84.4%) of study participants self-reported 6MP intake in excess of the electronic report at least some of the time, and almost one quarter (23.6%) of participants over-reported 6MP intake by 5 or more days in half or more of the study months. We found that there was only modest correlation between self-report and electronic monitoring. Furthermore, non-adherers were more likely to over-report 6MP intake (47%) as compared with adherers (8%).

Our finding that oral 6MP intake is over-reported compared to electronically-measured 6MP intake (92.6% by self-report vs. 83.7% by electronic monitoring) during the maintenance phase of therapy in children with ALL is consistent with literature in other pediatric chronic illness populations that require ongoing treatment with prescribed medications at home, including pediatric inflammatory bowel disease (intake of prescribed oral 6MP/azathioprine 90%

by parent/patient interview vs 36% by pill count);[11] adolescent bariatric surgery (post-operative oral multivitamin 88.4% by self-report vs. 37.4% by electronic monitoring);[12] HIV-infected children/youth (antiretroviral medication 100% by self-report vs. 75.4% by electronic monitoring);[13] and pediatric asthma (inhaled steroid 80% by self-/parent-report vs. 50% by electronic monitoring).[14] Previous reports in pediatric cancer patients have not directly compared self-report with electronic monitoring; however, reports of electronically monitored adherence rates have ranged from 71% to 95%,[2-4,9,10] whereas a single study that assessed adherence by a one-time self-reported interview reported an adherence rate of 70%.[6]

We found that patients of minority race/ethnicity and those from households with lower paternal education were more likely to over-report 6MP intake. This aligns with our previous studies, where we found children with ALL who are of Asian, Hispanic, or African American ancestry, as well as non-Hispanic white children from households with lower parental education, were more likely to be non-adherent to 6MP.[2,10] Our findings are also consistent with reports in other pediatric chronic illness populations that have shown minority race/ethnicity and lower parental educational level to be factors associated with poor medication adherence.[22-24]

Use of self-report to assess medication intake is simple and inexpensive, and is for this reason often used in clinical settings. On the other hand, the more sophisticated measures of medication adherence used in clinical trials (e.g., MEMS, drug assays, prescription refill records) may not be practical or readily available to the clinician in real time.[25] However, despite the simplicity and convenience of self-report for assessing medication adherence in the clinical setting, our findings suggest that self-report may not be a reliable measure, and are similar to findings of other studies examining this issue in non-oncology settings.[26-29] Use of self-report to monitor 6MP intake may erroneously lead clinicians to believe that patients are doing better at taking their 6MP than they actually are.

We found that the sensitivity of self-reported 6MP intake was low (i.e., 52.7%) while specificity was high (i.e., 95.8%) during maintenance therapy for ALL. These findings are similar

to studies focusing on other chronic illness populations, where self-report was associated with low sensitivity (i.e., patients who do not self-report their lack of intake of prescribed medications may go unrecognized) and high specificity (i.e., patients who self-report not taking prescribed medications are generally not taking them),[29,30] and self-report was poorly correlated with objective measures of medication intake.[29,31,32] In the current study, we found that only 12% of patients had "perfect" self-report records (i.e., self-report and MEMS records matched exactly); thus, 88% of patients inaccurately reported their 6MP intake, despite the fact that they knew that their 6MP intake was being electronically monitored throughout the study. We found that the large majority of the inaccurate reporting was over- rather than under-estimation of 6MP intake; and of particular concern was the finding that non-adherent patients were 9.4 times more likely to substantially over-report their 6MP intake (i.e., by 5 or more days in $\geq$50% of study months) when compared to adherent patients; thus, it may be extremely difficult for clinicians to discriminate adherent from non-adherent patients among those who report no or few missed doses.

This study needs to be considered in the context of its limitations. Although MEMS is considered the "gold standard" for objective monitoring of medication intake,[33] this electronic monitoring system cannot determine if the child actually swallowed their medication; we included red cell TGN levels in our models as an additional measure of chronic 6MP exposure. Self-report is also subject to bias due to parent/patient perception regarding responses considered acceptable or pleasing to the clinician (i.e., social desirability bias).[34] This study was designed such that the self-report was collected as part of a research questionnaire rather than directly by the patient's clinician; thus, social desirability bias may have played less of a role in this study than is typically seen in direct patient-clinician interactions. Nevertheless, it is possible that participants may have wished to please the study staff by providing favorable answers regarding adherence on the questionnaires, and thus the potential for social desirability bias must still be considered. Additionally, participants were requested to report their (their child's)

6MP intake over the past 28 days and thus it is possible that there was some recall bias. We also informed patients/parents that we were specifically monitoring adherence to 6MP, and it is possible that this knowledge could have altered their usual medication-taking behavior; however, previous research has shown that health behaviors tend to return to baseline shortly after initiation of monitoring,[35] and we followed patients over several months to account for this. Despite these limitations, this study had many strengths, including its longitudinal, prospective design, the large and diverse cohort assembled across 87 institutions, and the collection of 1,344 patient-months of both subjective and objective data regarding 6MP intake in the cohort, which allowed for a determination of the relation between self-report and electronic (MEMs) monitoring of 6MP intake in children with ALL during maintenance therapy.

In conclusion, we found that over-reporting of 6MP intake during maintenance therapy for childhood ALL is common, particularly in non-adherent patients. Furthermore, given that we have previously shown that 6MP non-adherence (as measured by MEMS) during maintenance therapy is associated with a significantly increased risk of relapse,[2,10] the poor (52.7%) sensitivity of self-reported 6MP intake raises cause for concern, particularly since self-report is commonly used for adherence assessment in clinical settings. Since accurate assessment of 6MP intake is crucial in order to identify non-adherent patients and ensure timely intervention, our findings suggest that alternate methods for identifying non-adherent patients in the clinical setting are needed. We are therefore currently developing a prediction tool to assist clinicians in identifying patients who are at increased risk for 6MP non-adherence, such that interventions can be targeted to the most vulnerable patients.

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Author Contribution

Smita Bhatia, Wendy Landier, and Mary Relling conceived and designed the study; Smita Bhatia, Wendy Landier, Lindsey Hageman, Bruce Bostrom, Jacqueline Casillas, David Dickens, Kelly Maloney, Leo Mascarenhas, A. Kim Ritchey, Amanda Termuhlen, and William Carroll acquired the data; Smita Bhatia, Yanjun Chen, F. Lennie Wong, Wendy Landier, Heeyoung Kim, William Evans, and Mary Relling analyzed and interpreted the data; Wendy Landier, Smita Bhatia, Lindsey Hageman, F. Lennie Wong, and Yanjun Chen drafted the manuscript. Smita Bhatia, Wendy Landier, Yanjun Chen, Lindsey Hageman, Heeyoung Kim, Bruce Bostrom, Jacqueline Casillas, David Dickens, William Evans, Kelly Maloney, A. Kim Ritchey, Amanda Termuhlen, William Carroll, F. Lennie Wong, and Mary Relling revised the manuscript for important intellectual content; F. Lennie Wong, Yanjun Chen, Heeyoung Kim, Wendy Landier, and Smita Bhatia performed statistical analysis; Smita Bhatia, Wendy Landier, Lindsey Hageman, and Mary Relling provided administrative, technical, or material support; Smita Bhatia, Wendy Landier, and Lindsey Hageman supervised the study.

Author Conflicts of interest

Drs. Bhatia, Landier, Bostrom, Casillas, Dickens, Maloney, Mascarenhas, Ritchey, Termuhlen, Carroll, Wong, Ms. Hageman, Ms. Kim, and Ms. Chen report no conflicts of interest.

St. Jude Children's Research Hospital allocates a portion of the income it receives from licensing inventions and tangible research materials to those researchers responsible for creating the intellectual property; Drs. Evans and Relling receive a portion of the income St. Jude receives from licensing patent rights related to testing for *TPMT* genetic polymorphisms.

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Table 1. Sociodemographic and Clinical Characteristics of Study Participants

Characteristic	Entire cohort (N=416)	Self-Report Phenotype		
		Perfect Reporter (N=50)*	Over-Reporter (N=98)†	*P*-value‡
Age at study participation (years)				
Median (range)	6 (2-20)	6 (2-19)	7 (2-20)	0.0311
Sex (n, %)				
Males	277 (66.6%)	35 (70%)	63 (64.3%)	0.49
Females	139 (33.4%)	15 (30%)	35 (35.7%)	
Race/ ethnicity (n, %)				
Non-Hispanic whites	148 (35.6%)	19 (38%)	18 (18.4%)	0.014
Hispanics	154(37.0%)	19 (38%)	42 (42.9%)	
Asians	56 (13.5%)	8 (16%)	13 (13.3%)	
African Americans	58 (13.9%)	4 (8%)	25 (25.5%)	
Annual Household Income (n, %)				
<$50K	238 (60.6%)	29 (59.2%)	65 (69.1%)	0.48
$50K-$100K	96 (24.4%)	11 (22.4%)	15 (16.0)	
>$100K	59 (15.0%)	9 (18.4%)	14 (14.9%)	
Maternal education (n, %)				
< college degree	231 (57.2%)	27 (54.0%)	58 (61.0%)	0.41
Paternal education (n, %)				
< college degree	242 (60.9%)	29 (59.2%)	68 (73.1%)	0.09
NCI risk group (n, %)[19]				
Standard risk	255 (61.6%)	32 (64%)	52 (53.6%)	0.23
High risk	159 (38.4%)	18 (36%)	45 (46.4%)	
Average 6MP Dose Intensity£				
Median (range)	0.86 (0.06-2.97)	0.87 (0.06-1.2)	0.91 (0.17-2.97)	0.066
***TPMT* genotype (n, %)**				
WT	389 (93.5%)	47(94%)	91(92.9%)	0.79
Average TGN levels (pmol/8 x 10^8 erythrocytes)				
Median (range)	147.3 (0.26-714.1)	157.2 (39.3-714.1)	136.3 (0.26-607.6)	0.0062
6MP Adherence¥				
Mean adherence rate	0.91	0.99	0.76	<0.0001
Non-adherers (n, %)	165 (39.7%)	0 (0.0%)	77 (78.6%)	<0.0001

* Perfect Reporters: No difference between self-report and MEMS for all study months

† Over-Reporters: Self-report exceeded MEMS report by ≥5 days in ≥50% of study months

‡ *P*-value for comparison of Over-Reporters to Perfect Reporters

£ 6MP Dose-Intensity: ratio of 6MP dose *actually* prescribed (mg/m^2 body surface area), to the planned protocol dose (75mg/m^2/day).

¥ 6MP Adherence Rate: Ratio of number of days with MEMS cap openings (X) to number of days 6MP was prescribed (N), reported as a percentage (X/N*100). 6MP Non-Adherence=MEMs-based adherence rate <95%

Statistics were calculated for this table by excluding patients with missing values for the characteristics.

Abbreviations: 6MP, 6-mercaptopurine; *TPMT,* thiopurine methyltransferase; TGN, erythrocyte thioguanine nucleotide concentrations; NCI, National Cancer Institute.

Table 2. Logistic regression analysis to identify predictors of subjective over-reporting by ≥5 days in ≥50% of study months (comparison group: all others)

	Univariable Analysis				Multivariable Analysis†			
		95% CI				95% CI		
Variable	OR	Lower	Upper	*P*	OR	Lower	Upper	*P*
Age (per year)	**1.07**	**1.018**	**1.125**	**0.0076**	1.079	0.991	1.175	0.0788
Race/Ethnicity								
Non-Hispanic white	1.000				1.000			
Hispanic	**2.733**	**1.489**	**5.017**	**0.0012**	**2.389**	**1.127**	**5.064**	**0.0231**
Asian	**2.235**	**1.011**	**4.944**	**0.0470**	**3.121**	**1.171**	**8.319**	**0.0229**
African-American	**5.471**	**2.673**	**11.198**	**<0.0001**	**5.389**	**2.274**	**12.775**	**0.0001**
Sex								
Male	1.000							
Female	1.132	0.704	1.821	0.6078				
Annual Household Income								
≥$50K	1.000							
<$50K	**1.629**	**0.993**	**2.671**	**0.0533**	1.118	0.574	2.178	0.7435
Maternal education								
≥ college degree	1.000							
< college degree	1.109	0.877	1.403	0.3873				
Paternal education								
≥ college degree	1.000				1.000			
< college degree	**1.43**	**1.107**	**1.847**	**0.0062**	**1.417**	**1.001**	**2.007**	**0.0493**
***TPMT* genotype**								
Wild type	1.000				1.000			
Heterozygous/homozygous	0.878	0.360	2.144	0.7757	0.879	0.501	1.543	0.6533
NCI risk classification								
Standard	1.000							
High	**1.526**	**0.963**	**2.418**	**0.0721**	0.887	0.419	1.876	0.7534
6MP Dose Intensity (per unit increase)	**3.914**	**1.386**	**11.051**	**0.0100**	1.276	0.363	4.480	0.7038
Red cell TGN level (per unit increase)	0.998	0.995	1.001	0.1881				
6MP MEMS adherence rate								
≥ 95% (adherent)	1.000				1.000			
<95% (non-adherent)	**9.651**	**5.613**	**16.595**	**<0.0001**	**9.407**	**5.066**	**17.467**	**<0.0001**

†Multivariable analysis includes variables from univariable analysis that were associated with over-reporting 6MP intake by $P<0.1$, adjusted for *TPMT* genotype.

Bold font indicates significance. Abbreviations: OR, Odds ratio; CI, Confidence interval; 6MP, 6-mercaptopurine; *TPMT*, thiopurine methyltransferase; TGN, thioguanine nucleotide; NCI, National Cancer Institute; MEMS, Medication Event Monitoring System

Figure Legend

Figure 1. Study schema

Figure 2. Medication Event Monitoring System (MEMS™) pill bottle and TrackCap®

Figure 3. Examples of MEMS data download:

3a: Patient with consistent 6MP intake across the study period (each blue dot represents one bottle opening).

3b: Patient with frequently missed 6MP doses taken at irregular intervals.

Figure 4: Adjusted mean days of 6MP intake by Generalized Estimating Equation analysis for self-report vs electronic (MEMS) monitoring for the entire cohort by study month

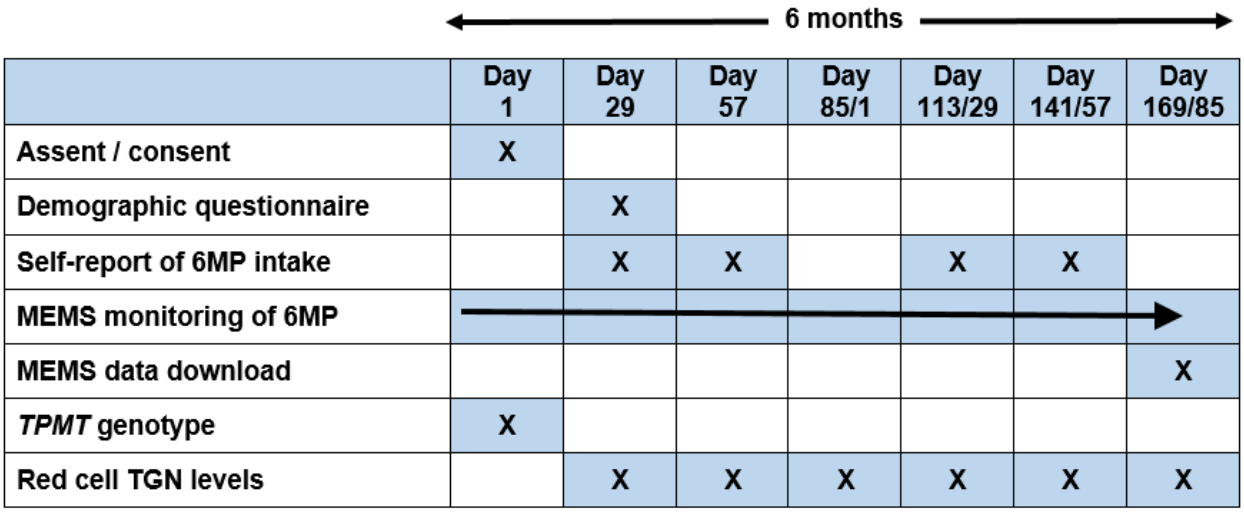
Figure 5: Adjusted mean days of 6MP intake by Generalized Estimating Equation analysis for self-report vs electronic (MEMS) monitoring by study month stratified by:

5a: Racial/Ethnic Groups (Non-Hispanic Whites, Hispanics, Asians, African Americans)

5b: Paternal Education ($\geq$ college degree and < college degree)

5c: 6MP Adherence Rate ($\geq$95% and <95%)

Figure 1.



Abbreviations: 6MP, 6-mercaptopurine; MEMS, Medication Event Monitoring System; *TPMT,* thiopurine methyltransferase; TGN, erythrocyte thioguanine nucleotide concentrations

Figure 2.

Figure 3.

Figure 3a.

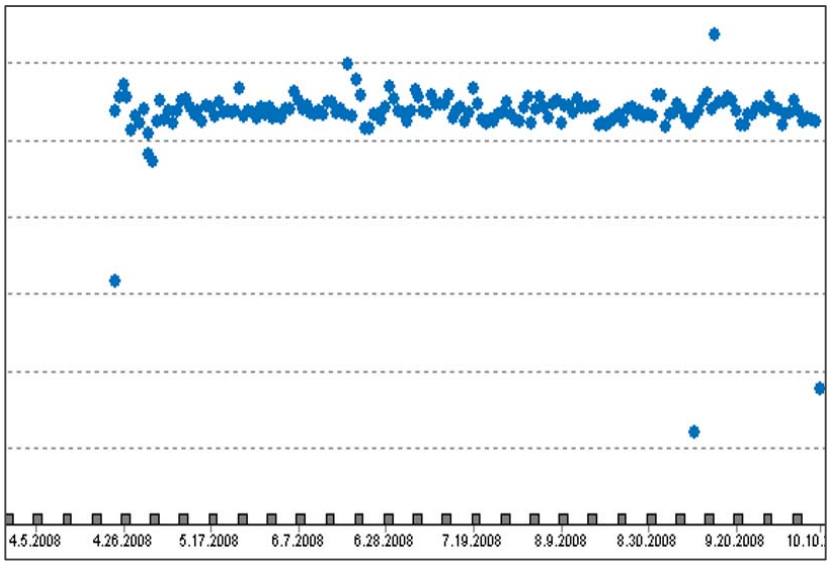


Figure 3b.

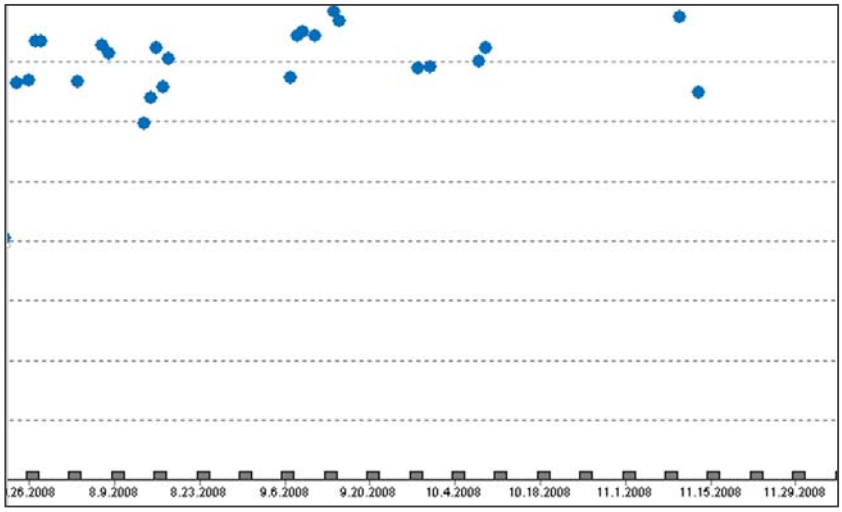
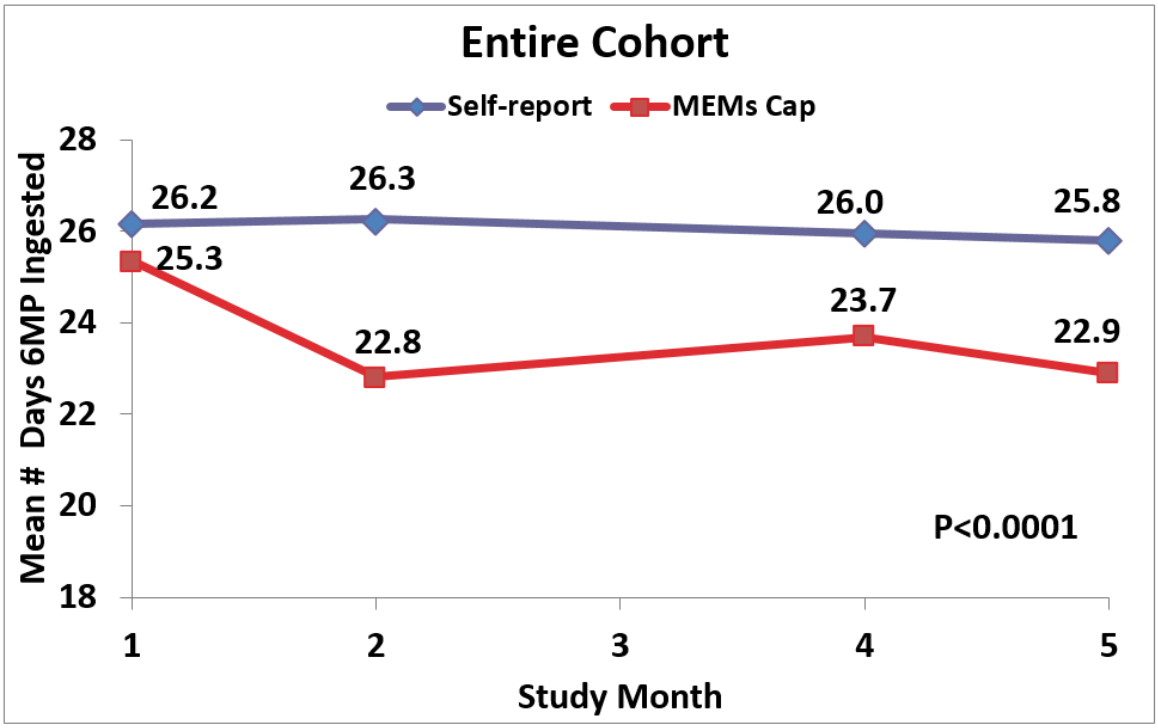
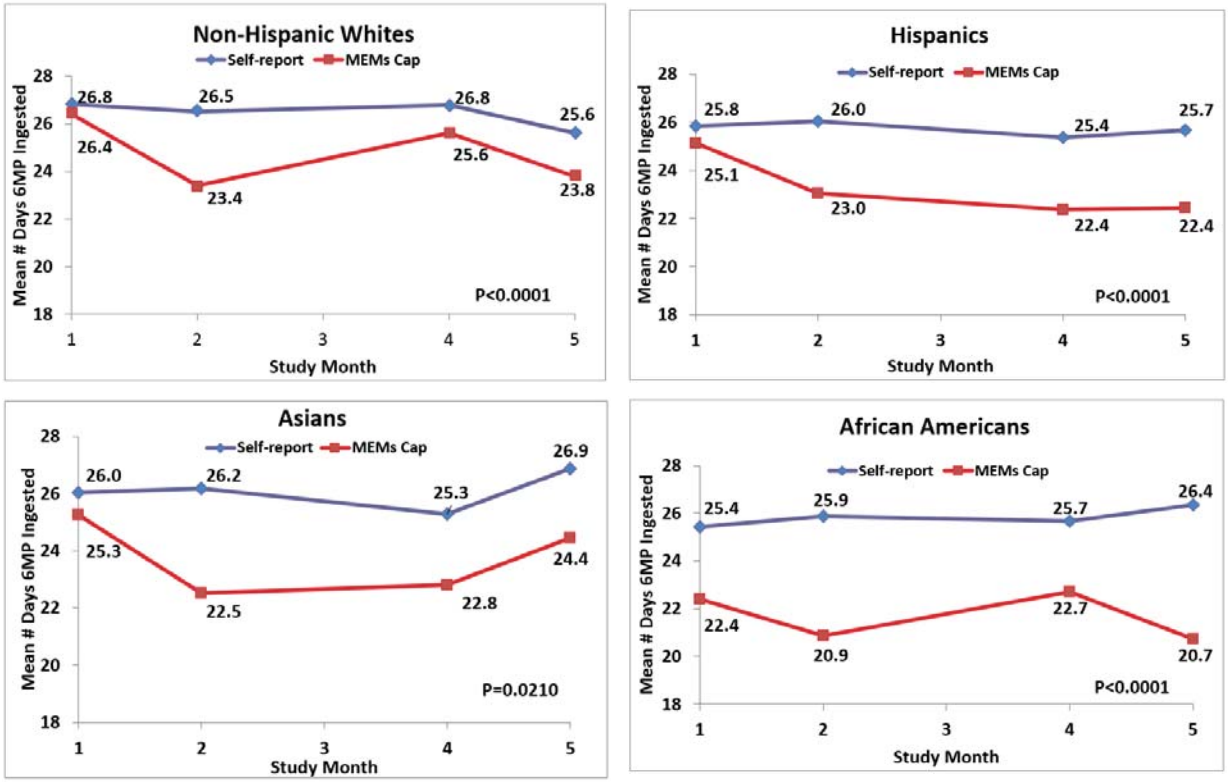


Figure 4.



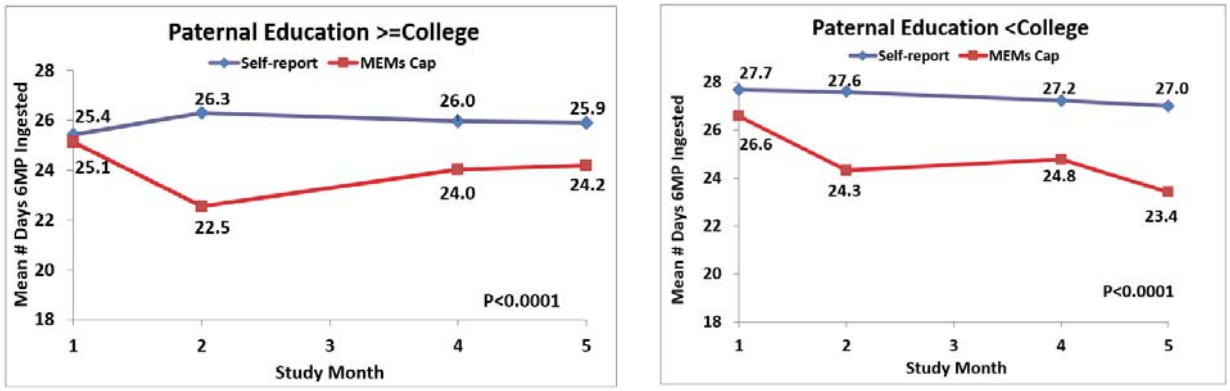
Adjusted mean values by generalized estimating equation analysis

Figure 5a.



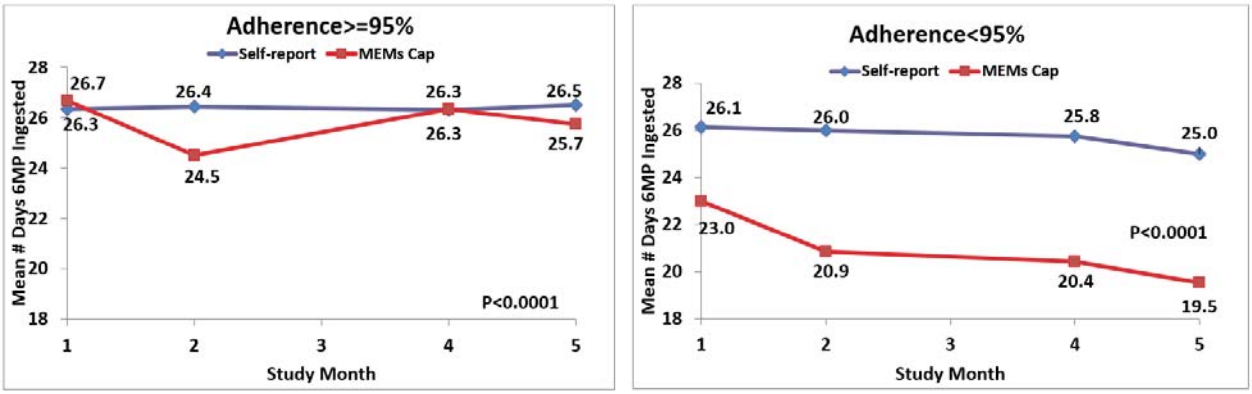
Adjusted mean values by generalized estimating equation analysis

Figure 5b.



Adjusted mean values by generalized estimating equation analysis

Figure 5c.



Adjusted mean values by generalized estimating equation analysis

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Comparison of self-report and electronic monitoring of 6MP intake in childhood ALL: A Children's Oncology Group study

Wendy Landier, Yanjun Chen, Lindsey Hageman, Heeyoung Kim, Bruce C. Bostrom, Jacqueline N. Casillas, David S. Dickens, William E. Evans, Kelly W. Maloney, Leo Mascarenhas, A. Kim Ritchey, Amanda M. Termuhlen, William L. Carroll, Mary V. Relling, F. Lennie Wong and Smita Bhatia

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