ARTICLE

A Video Game Improves Behavioral Outcomes in Adolescents and Young Adults With Cancer: A Randomized Trial

Pamela M. Kato, PhD, EdM[a,b], Steve W. Cole, PhD[b], Andrew S. Bradlyn, PhD[c], Brad H. Pollock, PhD, MPH[d]

[a]Department of Pediatrics, Stanford Hospital, Stanford, California; [b]HopeLab Foundation, Redwood City, California; [c]Health Research Center, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, West Virginia; [d]Department of Epidemiology and Biostatistics, School of Medicine, and San Antonio Cancer Institute, University of Texas Health Science Center, San Antonio, Texas

The authors have indicated they have no financial relationships relevant to this article to disclose.

What's Known on This Subject

Adherence is a significant problem when managing chronic illness. There is some evidence that video games and/or interactive multimedia tools can help to improve health-related behaviors in pediatric populations, but conclusions from these studies have been tentative because of small study size and inadequate controls.

What This Study Adds

To our knowledge, this is the first large-scale, randomized, intervention trial, pharmaceutical or behavioral, conducted with a study population composed exclusively of AYA with cancer. The intervention focuses on treatment adherence, a pervasive problem in this age group in general.

ABSTRACT

OBJECTIVE. Suboptimal adherence to self-administered medications is a common problem. The purpose of this study was to determine the effectiveness of a video-game intervention for improving adherence and other behavioral outcomes for adolescents and young adults with malignancies including acute leukemia, lymphoma, and soft-tissue sarcoma.

METHODS. A randomized trial with baseline and 1- and 3-month assessments was conducted from 2004 to 2005 at 34 medical centers in the United States, Canada, and Australia. A total of 375 male and female patients who were 13 to 29 years old, had an initial or relapse diagnosis of a malignancy, and currently undergoing treatment and expected to continue treatment for at least 4 months from baseline assessment were randomly assigned to the intervention or control group. The intervention was a video game that addressed issues of cancer treatment and care for teenagers and young adults. Outcome measures included adherence, self-efficacy, knowledge, control, stress, and quality of life. For patients who were prescribed prophylactic antibiotics, adherence to trimethoprim-sulfamethoxazole was tracked by electronic pill-monitoring devices ($n = 200$). Adherence to 6-mercaptopurine was assessed through serum metabolite assays ($n = 54$).

RESULTS. Adherence to trimethoprim-sulfamethoxazole and 6-mercaptopurine was greater in the intervention group. Self-efficacy and knowledge also increased in the intervention group compared with the control group. The intervention did not affect self-report measures of adherence, stress, control, or quality of life.

CONCLUSIONS. The video-game intervention significantly improved treatment adherence and indicators of cancer-related self-efficacy and knowledge in adolescents and young adults who were undergoing cancer therapy. The findings support current efforts to develop effective video-game interventions for education and training in health care. *Pediatrics* 2008;122:e305–e317

www.pediatrics.org/cgi/doi/10.1542/peds.2007-3134

doi:10.1542/peds.2007-3134

This trial has been registered at www.clinicaltrials.gov (identifier NCT00425139).

This study was presented in part at the annual meeting and scientific sessions of the Society for Behavioral Medicine, March 22–25, 2006, San Francisco, CA; the Teenage Cancer Trust Fourth International Conference on Teenage and Young Adult Cancer Medicine, March 30–31, 2006, London, England; and the 11th annual Cyber Therapy Conference, June 12–15, 2006, Gatineau, Quebec, Canada.

Key Words

adherence, cancer, video game, adolescent, pediatric oncology, randomized trial

Abbreviations

AYA—adolescents and young adults
6-MP—6-mercaptopurine
TMP/SMX—trimethoprim-sulfamethoxazole
6MMP—methylmercaptopurine nucleotides
6-TG—6-thioguanine nucleotides
MEMS—Medication Event Monitoring System
CDCI—Chronic Disease Compliance Instrument

Accepted for publication Apr 7, 2008

Address correspondence to Pamela M. Kato, PhD, EdM, University Medical Center Utrecht, Center for Patient Safety, Housepost number Q 05.4.300, PO Box 85500, 3508 GA Utrecht, Netherlands. E-mail: pkato@umcutrecht.nl

PATIENT NONADHERENCE TO treatment regimens is an ongoing problem in the practice of medicine in general.[1] It is widely known that adolescents and young adults (AYA) with cancer often fail to adhere to prescribed treatment regimens, especially self-administered treatments such as oral chemotherapy.[2–7] This is a significant challenge to overcome especially in light of the fact that cancer incidence for AYA has increased over time to become the leading cause of nonaccidental death in this age group.[8,9] Development of effective treatment protocols in the past 2 decades has dramatically reduced childhood cancer mortality rates, but AYA have not shown comparable benefits.[9] Suboptimal treatment adherence is believed to contribute to this disparity.[10–14] Intensive behavioral interventions involving

1-on-1 instruction and nurse home visits have been shown to increase adherence[15] and affect survival among patients with cancer.[16] A more efficient and easily distributed adherence intervention targeted to the needs of this particular patient population may hold promise for improving clinical disease outcomes in this group and provide a model for addressing noncompliance in other disease groups as well.

Several cognitive and motivational processes are hypothesized to affect treatment adherence, including knowledge about the therapy and its relationship to health,[2,13,17,18] perceptions of one's ability to influence health outcomes (perceived control),[19,20] and confidence in one's ability to meet the specific demands of cancer treatment and recovery (cancer-specific self-efficacy).[21–24] Previous interventions have sought to affect these psychological determinants of patient behavior by using traditional didactic learning strategies. The approach explored in this study exploits new opportunities for learning and improving health outcomes through video-game technology.

Video games may provide several advantages over didactic teaching as tools for affecting health behaviors, including vicarious practice of target skills, complex problem-solving, contingency-based learning of targeted information, and procedural knowledge in an interactive format.[25–27] Conventional video games have been used as intervention tools for health mostly as a means of distraction for pain.[28] Video-game–based interventions have been specifically developed for asthma,[27,29,30] diabetes,[31–33] cystic fibrosis,[34] and cancer.[35,36] Clinical studies have linked game use to indicators of effective disease management, including blood glucose levels,[37] self-care behaviors,[33,37] symptom management,[29] self-efficacy,[27] disease-related knowledge,[27,29,34] and emergency department use.[29] Conclusions from these studies are suggestive but tentative because of small study size and inadequate controls (with some exceptions[29,33,34]).

On the basis of theories of video-game–based learning and suggestive evidence that video games can improve health-related behavior in other contexts, we developed a video game for AYA with cancer. Behavioral objectives were translated into game structure on the basis of principles from the self-regulation model of health and illness,[38–42] social cognitive theory,[43] and learning theory.[44–46] We report the results from a multicenter, randomized trial that tested the efficacy of this intervention to improve adherence to prescribed treatment regimens and other health-related behavioral outcomes in AYA who were undergoing active treatment for cancer.

METHODS

Participants

Patients were recruited by fliers and staff contact at 34 academic medical centers and community practices in the United States, Canada, and Australia. Participation was open to patients who were aged 13 to 29 years and had a malignancy diagnosis (newly diagnosed or relapsed) and were undergoing treatment (chemotherapy, radiation, or stem cell transplantation) that was expected to last at least 4 months after enrollment. Exclusion criteria were a history of seizures as a result of photosensitivity (eg, flashing lights); inability to communicate with study personnel in English, French, or Spanish; or inability to follow the study schedule or directions.

Written informed consent was obtained from adult participants or from a minor's parent or legal guardian. Information on race/ethnicity was provided by patient self-report. All procedures were approved by local institutional review boards.

Study Design

This 2-arm randomized trial assessed the incremental effect of playing the cancer-targeted video-game intervention over and above any general effect of playing a video game. After baseline assessment, all participants received a Shuttle SB51G mini-computer (Shuttle, Inc, Taiwan) that contained a commercial game alone (control group) or the same commercial game plus the intervention game (intervention group). Participants were asked to play the game(s) for at least 1 hour per week during the 3-month study period, and serial outcome assessments were collected at 1 and 3 months after baseline. Game use was recorded electronically, and computers were retrieved after study completion.

Randomization

After baseline assessments, a site associate contacted a study coordinator at a central office, who gave the associate a number indicating a specific computer to be distributed to the participant (ie, a computer implementing the control or experimental condition). Computer allocation was randomized within sites (as blocks) on the basis of a computerized random-number generator. Condition assignment of each participant was concealed from study personnel, but participants became aware of their treatment assignment once they logged onto their assigned computers.

The Intervention Game

Re-Mission[47] (www.re-mission.net) is a PC game in which players control a nanobot, "Roxxi," in 3-dimensional environments within the bodies of young patients with cancers that commonly are diagnosed in AYA (acute lymphoblastic leukemia, acute myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, osteosarcoma, Ewing sarcoma, and brain tumors). Game content was engineered to address behavioral issues that were identified in literature reviews and preproduction targeting studies[48–54] as critical for optimal AYA patient participation in cancer treatment. Video-game play includes destroying cancer cells and managing common treatment-related adverse effects such as bacterial infections, nausea, and constipation by using chemotherapy, antibiotics, antiemetics, and a stool softener as ammunition. To win, players control the nanobot, Roxxi, to ensure strategically that virtual patients engage in positive self-care behaviors, such as taking oral chemotherapy to fight cancer cells, taking antibiotics to fight infection, taking stool soft-

TABLE 1 **Description of Measures of Primary and Secondary End Points**

Measures	Type of Measure	Description	Cronbach's α[a]
Primary end points			
CDCI[57]	Self-report	A measure of adherence to medical treatment of young people with cancer, translated and adapted from the original Finnish version of the scale.[56,57] On this 18-item scale, responses are rated on a scale from 1 to 5, and total scores range from 18 to 90.	.83
MAS[58]	Self-report	A measure of general adherence to medical treatment. This is a 4-item scale with yes/no questions; scores range from 0 to 4 with higher scores representing greater adherence.	.57
Clinic Visit Attendance	Objective	Scores reflect percentage of clinic visits missed as tracked by study associates.	NA
MEMS[59,60]	Objective	A measure of adherence to TMP/SMX (Septra, Bactrim, cotrimoxazole) for patients prescribed this drug for antimicrobial prophylaxis. The MEMS consists of a medication container with a cap that contains a microprocessor that records the dates and times the container is opened.	NA
6-MP blood assays	Objective	Blood metabolites of 6MMP and 6-TG provide an indication of adherence to 6-MP. Assays are performed on duplicate samples at a central laboratory with a standard high-performance liquid chromatography assay.[61]	NA
Secondary end points			
Self-efficacy Scale	Self-report	A measure of one's confidence in his or her ability to carry out specific behaviors to reach a goal according to Social Cognitive Theory.[62] This measure was constructed in accordance with the standard method for designing self-efficacy scales.[63,64] As such, it was designed specifically for this study to assess self-efficacy beliefs targeted in the intervention game. Responses on this 27-item scale are rated on a Likert scale of 1 to 7, where total scores reflect the average rating of all items (maximum score: 7) with higher scores indicating greater perceived self-efficacy to manage cancer and its treatment (see Appendix 1).	.93
Cancer Knowledge Scale	Self-report	Developed specifically for this study as a measure of patients' knowledge about cancer as delivered in the intervention game. In this 18-item multiple-choice questionnaire, total scores range from 0% to 100%, with higher scores indicating greater cancer-related knowledge (see Appendix 2).	NA
PQL—Generic Core Scale Version 4.0[65]	Self-report	A measure of physical and psychological quality of life of children aged 13–18. The 23 items on this scale are made up of 8 physical quality of life items and 15 psychological quality of life items. Items are rated on a scale of 0 to 4 and are transformed linearly to a 0 to 100 scale for scoring. Higher scores indicate a greater quality of life.	.91
FACT-G[66,67]	Self-report	A measure of the functional status of patients aged ≥18 with cancer. The 27 items are rated on a Likert scale of 0 to 4. The total FACT-G score is the summation of the 4 subscale scores and ranges from 0 to 108.	.92
Multidimensional Health Locus of Control Scale Form C[68]	Self-report	This 18-item scale is a measure of patients' perceptions of sources of control over their health. All items are rated on a scale of 1 to 6, and scores are calculated for 5 subscales that indicate the patient's perception of control in relation to different sources of influence (ie, self, chance, powerful others, doctors, other people). The total scores for the subscales range from 3 to 36, with higher scores indicating higher locus of control.	.56–.77
Perceived Stress Scale 10[69]	Self-report	This 10-item scale measures the degree to which situations in one's life are appraised as stressful. Items are rated on a scale of 1 to 5, and total scores range from 10 to 50 with higher scores indicating more stress.	.85

NA indicates not available; PQL, Pediatric Quality of Life Inventory; FACT-G, Functional Assessment of Cancer Therapy–General.

[a] Cronbach's α is an indicator of construct validity. Coefficients were calculated from baseline data in this sample.

eners to prevent bowel perforations, practicing good mouth care to combat mucositis, using relaxation techniques to reduce stress, and eating food to gain energy. Neither the nanobot nor any of the virtual patients "die" in the game. If players "fail" at any point in the game, then the nanobot powers down and players are given the opportunity to try the mission again. Players had to complete missions successfully before moving on to the next level.

The Commercial Game

A PC version of Indiana Jones and the Emperor's Tomb[55] served as the control game because the play structure and controller interface closely resembled that of Re-Mission.

Study End Points

The primary end point was adherence to prescribed cancer treatment regimen (including assessment of plasma 6-mercaptopurine [6-MP] metabolites by HPLC [Prometheus Laboratories, San Diego, CA] and Medication Event Monitoring System (MEMS)-cap electronic monitoring of trimethoprim-sulfamethoxazole [TMP/SMX] use [Aprex, San Diego, CA]). Secondary end points included self-efficacy to manage cancer, knowledge about cancer, health locus of control, stress, and quality of life. Self-report measures were available in English, Spanish, or Canadian French and translated when necessary. Standard procedures were used to translate these documents.[56] Table 1 describes each measure.

Statistical Methods

Sample size was estimated on the basis of a previous 38-patient pilot study conducted at Stanford University and the University of Texas Health Science Center at San Antonio. Analyses targeted detection of an effect size of

0.2 SD with 80% power and $\alpha = .05$ (2-sided), with adjustment for an anticipated 20% attrition rate.

Statistical analyses were conducted on an intention-to-treat basis using SAS 9.1.3 (SAS Institute, Inc, Cary, NC). Primary analyses used a repeated-measures mixed-effect linear model testing differences between treatment groups at 3 time points in a 2 (treatment) × 3 (time) factorial design (SAS PROC MIXED). Intervention effects on outcome trajectories over time were gauged by the treatment × time interaction term. Analyses that adjusted for effects of gender, age at study entry, and interval between entry and diagnosis (or relapse) did not alter primary conclusions (data not shown).

Primary analyses also adjusted for game system use by including an indicator variable ("anyplay": 1 = played the game(s) at least once; 0 = never played). The anyplay × treatment interaction term assessed whether treatment effects were greater for those who accessed the game system versus not at all.

TMP/SMX (MEMS) dose count data were analyzed using Poisson regression adjusting for individual differences in prescribed numbers of antibiotic doses (SAS PROC GENMOD).

Blood 6-MP metabolite values (methylmercaptopurine nucleotides [6MMP] and 6-thioguanine nucleotides [6-TG]) were log-transformed and analyzed using mixed-effect linear modeling as described. Observations that were conducted when participants were not scheduled to take 6-MP were excluded from analysis. Analyses examined 6MMP and 6-TG levels as separate indicators of 6-MP consumption (2 metabolite × 2 condition × 3 time analysis) and, alternatively, as the arithmetic sum of the 2 metabolites to estimate total 6-MP consumption.

To test the hypothesis that the effects of the intervention on primary outcomes (adherence) were mediated by changes in secondary outcomes (knowledge and/or self-efficacy), we conducted standard multivariate mediation analyses as previously described.[70] Mediation analyses of TMP/SMX adherence during 3 months of follow-up compared the effects of intervention condition on primary outcomes in an unmediated model with the effects observed in a mediated model that controlled for changes between baseline and the average of 1- and 3-month follow-up scores of the secondary outcomes (treated as mediators). As described,[70] mediation was indicated by a significant intervention effect in an unmediated model that changed to a nonsignificant intervention effect in a mediated model (ie, the residual significance of the intervention effect when controlling for candidate mediator). Similar mediation analyses were conducted for 6-MP metabolite levels, with the total effect of experimental conditions quantified by statistical significance of the condition × time interaction term as described, and the residual effect was quantified by the significance of the same interaction term after controlling for simultaneous changes in the value of a candidate mediator. The 2-degrees-of-freedom intervention condition × time interaction term simultaneously tests changes from baseline to 1-month follow-up and from baseline to 3-month follow-up while controlling for changes in the value of the mediator from baseline to 1-month follow-up and baseline to 3-month follow-up, respectively.[71]

RESULTS

Study Population

A total of 533 AYA with cancer were screened for study eligibility (Fig 1) from October 2004 to July 2005 at 34 medical centers in the United States ($n = 27$), Canada ($n = 6$), and Australia ($n = 1$). Among the 479 participants who were eligible, 375 were enrolled. Data for 4 participants were subsequently excluded because of inadequate consent documentation, withdrawal of consent, or determination of an ineligible diagnosis, leaving a final study population size of 371. The English version of the study materials was administered to 90% of the study population, the French version to 8.4%, and the Spanish version to 1.3%. Characteristics of the 2 treatment groups did not differ significantly at baseline (Table 2).

Attrition and Intervention Adherence

As shown in Fig 1, groups showed similar attrition rates during the 3-month study (17% of intervention group participants and 21% of control participants). Study computers, recovered from all but 1% of participants ($n = 4/371$), indicated an average of 7.7 hours (SE: ±1.0) of use among control group members and 10.7 (±1.0) hours among intervention group members (2-sample t test, $P = .042$). Twenty-two percent of the control group and 33% of the intervention group used their computers for the requested duration of at least 1 hour per week (χ^2 test, $P = .021$). Nine percent of control group participants and 13% of intervention group participants did not play their assigned game(s) at all ($P = .22$), and these individuals were more likely to be nonwhite (15% nonwhite vs 8% white; $P = .049$). African American participants showed the highest nonuse rates (18%, difference from white participants: $P = .051$), and when data were stratified according to condition, African American participants showed increased nonuse rates only in the treatment group ($P = .0086$). African American ethnicity was not associated with nonuse of the game in the control group ($P = .52$). Nonuse rates for Hispanic participants (4%) and participants of mixed or other ethnicity (10%) did not differ significantly from those of white participants (both $P > .58$). In addition, participants who did not play their games at all were more likely to have failed to complete all study visits (ie, skip a study visit or withdraw from the study early; $P = .0009$). This was true in both the treatment and control groups (treatment group $P = .0071$; control group $P = .0066$). African American participants were no more likely to have failed to complete all study visits than other ethnic groups ($P = .66$). Nonuse did not vary as a function of history of video-game play experience before the cancer diagnosis, cancer diagnosis, or sociodemographic factors other than African American ethnicity.

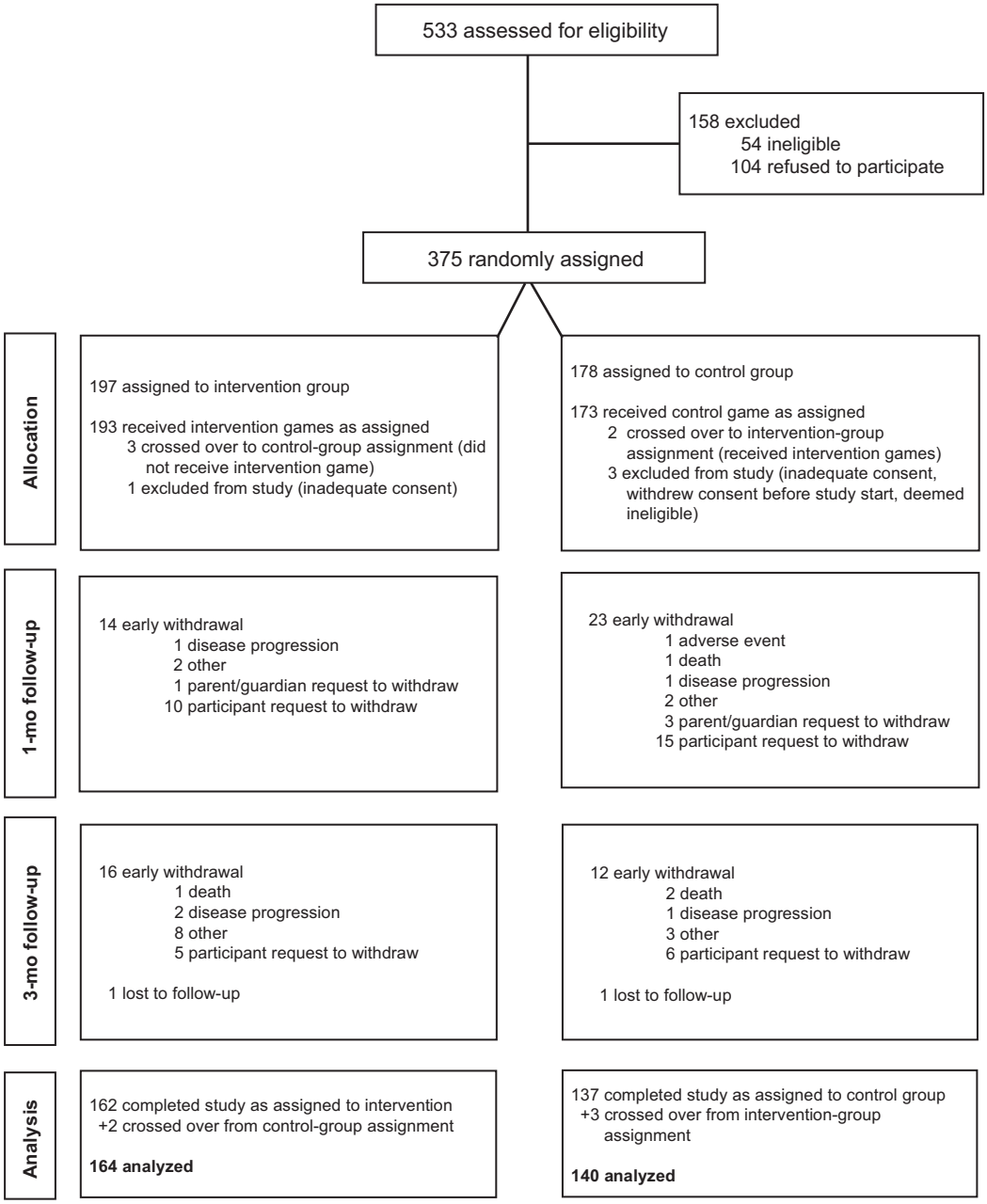

FIGURE 1
Study flow diagram.

Primary Outcomes

Table 3 contains the unadjusted means for each study outcome.

General Treatment Adherence

Self-reported adherence did not differ significantly between groups as measured by the Medication Adherence Scale (group × time interaction, $P = .503$) or the Chronic Disease Compliance Instrument (CDCI) (difference, $P = .78$). Participants in both groups reported uniformly high treatment adherence across assessment time points. Oncology clinic visit attendance was high for both groups (mean: 98 ± 1% of scheduled visits for both intervention and control) and did not differ significantly (Poisson regression for count data, controlling for individual differences in the number of clinic visits scheduled, $P = .65$).

Antibiotic Adherence

Among 200 participants who were prescribed oral TMP/SMX, MEMS-cap monitoring indicated a 16% increase in adherence for intervention group participants (intervention mean: 34.4 ± 2.5 doses; control mean: 29.5 ± 2.6 doses; Poisson regression controlling for individual variation in the prescribed number of doses, $P = .012$; Fig 2A), which corresponds to 62.3% of total prescribed

TABLE 2 **Baseline Participant Characteristics**

Characteristics	Participants, *n* (%)[a]			*P*[b]
	Intervention (*n* = 195)	Control (*n* = 176)	Total Population (*N* = 371)	
Age, y				
13–14	71 (36.4)	60 (34.1)	131 (35.3)	
15–16	56 (28.7)	58 (32.9)	114 (30.7)	.34
17–18	47 (24.1)	32 (18.2)	79 (21.3)	
19–29	21 (10.8)	26 (14.8)	47 (12.7)	
Gender				
Male	132 (67.7)	119 (67.6)	251 (67.7)	.99
Female	63 (32.3)	57 (32.4)	120 (32.3)	
Race/ethnicity				
White	109 (55.9)	101 (57.4)	210 (56.6)	
Hispanic	42 (21.5)	34 (19.3)	76 (20.5)	
Black/African American	19 (9.7)	15 (8.5)	34 (9.2)	
Mixed	9 (4.6)	6 (3.4)	15 (4.0)	
Asian	4 (2.1)	6 (3.4)	10 (2.7)	.40
Native American	2 (1.0)	1 (0.6)	3 (0.8)	
Pacific Islander	0 (0.0)	3 (1.7)	3 (0.8)	
Decline to answer	6 (3.1)	2 (1.1)	8 (2.2)	
Missing	4 (2.1)	8 (4.5)	12 (3.2)	
Education				
Less than high school	76 (39.0)	57 (32.4)	133 (35.8)	
High school	81 (41.5)	77 (43.8)	158 (42.6)	.39
Some college or more	33 (16.9)	33 (18.8)	66 (17.8)	
Not stated	5 (2.6)	9 (5.1)	14 (3.8)	
Annual family income, $[c]				
<10 000	11 (5.6)	17 (9.7)	28 (7.6)	
10 000–19 999	21 (10.8)	18 (10.2)	39 (10.5)	
20 000–39 999	35 (17.9)	24 (13.6)	59 (15.9)	
40 000–59 999	29 (14.9)	20 (11.4)	49 (13.2)	.29
60 000–79 999	15 (7.7)	22 (12.5)	37 (9.9)	
80 000–99 999	16 (8.2)	8 (4.6)	24 (6.5)	
≥100 000	22 (11.3)	18 (10.2)	40 (10.8)	
Declined to answer	46 (23.6)	48 (27.3)	94 (25.3)	
Don't know	0 (0.0)	1 (0.6)	1 (0.3)	
Country of residence				
United States	157 (80.5)	146 (83.0)	303 (81.7)	
Canada	31 (15.9)	27 (15.3)	58 (15.6)	.52
Australia	7 (3.6)	3 (1.7)	10 (2.7)	
Malignancy diagnosis				
Acute lymphoblastic leukemia	76 (38.9)	74 (42.1)	150 (40.4)	
Acute myelogenous leukemia	15 (7.7)	15 (8.5)	30 (8.1)	
Hodgkin's lymphoma	19 (9.7)	16 (9.1)	35 (9.4)	
Non-Hodgkin's lymphoma	17 (8.7)	9 (5.1)	26 (7.0)	.91
Brain tumor	14 (7.2)	14 (7.9)	28 (7.6)	
Osteosarcoma	24 (12.3)	18 (10.2)	42 (11.3)	
Ewing sarcoma	9 (4.6)	10 (5.7)	19 (5.1)	
Other	21 (10.8)	20 (11.4)	41 (11.1)	
Previous disease (relapse/recurrence)				
0	152 (77.9)	136 (77.3)	288 (77.6)	
1	27 (13.9)	30 (17.1)	57 (15.4)	
2	10 (5.1)	8 (4.6)	18 (4.9)	.66
3	4 (2.1)	1 (0.6)	5 (1.4)	
4	2 (1.0)	1 (0.6)	3 (0.8)	
Time since diagnosis for the group without relapse (*n* = 288)				
Median (range), y	0.72 (0.01–15.10)	0.65 (0.01–12.30)	0.69 (0.01–15.14)	
Mean (SD), y	1.53 (2.3)	1.67 (2.5)	1.59 (2.4)	.56
Time since most recent relapse/recurrence (*n* = 83)				
Median (range), y	0.50 (0.01–7.50)	0.45 (0.01–11.80)	0.48 (0.01–11.80)	
Mean (SD), y	0.79 (0.93)	0.84 (1.40)	0.82 (1.20)	.67

TABLE 2 **Continued**

Characteristics	Participants, *n* (%)[a]			*P*[b]
	Intervention (*n* = 195)	Control (*n* = 176)	Total Population (*N* = 371)	
Video-game play history before malignancy diagnosis, h/wk				
No game play	26 (13.3)	22 (12.5)	48 (12.9)	
<1	39 (20.0)	35 (19.9)	74 (20.0)	
1–3	58 (29.7)	49 (27.8)	107 (28.8)	.86
3–8	36 (18.5)	35 (19.9)	71 (19.1)	
≥8	31 (15.9)	26 (14.8)	57 (15.4)	
Missing	5 (2.6)	9 (5.1)	14 (3.8)	

[a] Percentages may not sum to 100% because of rounding.

[b] Test of association from χ^2 test (categorical variables), excluding categories of missing values, or independent *t* test of log-transformed values (continuous variables).

[c] In US dollars.

TMP/SMX doses taken by intervention participants versus 52.5% taken by control participants.

Oral Chemotherapy Adherence

Fifty-four patients were prescribed oral 6-MP as therapy for acute leukemia ($n = 51$) or non-Hodgkin's lymphoma ($n = 3$). Mixed-effect linear model analyses of log-transformed 6MMP concentrations showed that patients in the intervention group maintained significantly higher chemotherapy metabolite levels over time than did patients in the control group (significant group × time interaction; $P = .002$; Fig 2B). Analyses of 6-TG showed a similar pattern but did not reach statistical significance as a result of greater individual variability in blood metabolite levels (Fig 2C). When 6MMP and 6-TG concentrations were analyzed in a single model as distinct indicators of 6-MP metabolism (group × time × metabolite design), a significant group × time interaction also emerged ($P = .041$). Similar results also emerged when data were dichotomized at 6MMP ≤1000 pmol/8 × 10^8 red blood cells (an empirical break point in the 6MMP distribution distinguishing minimal values associated with nonadherence from higher ranging values that likely reflect individual differences in 6-MP metabolism; group × time interaction, $P < .001$). Baseline values of 6MMP or 6-TG did not differ between intervention and control groups (baseline 6MMP $P = .562$; baseline 6-TG $P = .981$).

Self-report Versus Objective Measures of Treatment Adherence

Posthoc correlation analyses (adjusted for multiple comparisons with the Bonferroni correction) were conducted to examine the relationship between self-report measures of adherence (ie, the Medication Adherence Scale and CDCI) and objective measures of adherence (ie, MEMS data and 6-MP metabolite levels). Analyses were conducted on self-report total scores and individual item scores within each measure at each follow-up point and correlated with MEMS percentage of dose taken and 6-MP metabolite levels at each follow-up point. We examined these correlations within study conditions as well. Results revealed no significant relationship between self-report and objective measures of adherence with the exception of 2 items on the CDCI that were related to MEMS assessment of TMP/SMX adherence. On 1 item, patients were asked to rate the extent to which they agreed with the statement, "I feel I am responsible for following my treatment plan as instructed." Patients who agreed with this statement more at the 3-month follow-up than at baseline showed poorer adherence to TMP/SMX (Spearman $r = -0.266$, $P = .0004$). This finding did not hold when each study condition was analyzed separately. For the treatment group, patient agreement with this statement at the 3-month follow-up was associated with greater adherence to TMP/SMX ($r = 0.439$, $P < .0001$) for the duration of the study. Similarly, patients in the treatment group who agreed with the statement, "I have followed the recommended diet," more at the 1-month follow-up compared with baseline showed greater adherence to TMP/SMX ($r = 0.489$, $P = .0006$). No CDCI items were associated with adherence for patients in the control group.

Secondary Outcomes

Cancer-Related Knowledge

Mixed-effect linear model analyses indicated comparable baseline levels of cancer-related knowledge for both groups and a significantly greater increase in cancer-related knowledge over time in the intervention group (group × time interaction, $P = .035$; Fig 3A).

Cancer-Specific Self-efficacy

Mixed-effect linear model analyses indicated similar levels of cancer-specific self-efficacy in intervention and control group participants at baseline but significantly greater increase in self-efficacy over time for members of the intervention group (group × time interaction, $P = .011$; Fig 3B).

Quality of Life, Stress, and Control

Quality of life as assessed by the Pediatric Quality of Life self-report instrument (for participants younger than 18 years) and the Functional Assessment of Cancer Therapy–

TABLE 3 **Observed Means (Raw) of Outcomes at Baseline and Follow-ups According to Study Group**

Outcome Variable	Intervention Group			Control Group		
	Baseline	1 Mo	3 Mo	Baseline	1 Mo	3 Mo
Self-report adherence						
CDCI						
Mean (SD)	79.2 (7.9)	79.0 (8.3)	81.0 (8.7)	77.4 (7.5)	78.4 (7.7)	78.4 (7.5)
n	191	172	163	167	147	140
MAS						
Mean (SD)	2.9 (1.1)	3.0 (1.1)	2.9 (1.1)	2.9 (1.1)	3.1 (1.0)	3.0 (1.1)
n	190	167	160	166	146	138
Adherence to TMP/SMX, % of prescribed doses taken,						
Mean (SD)			62.3 (62.9)			52.5 (37.6)
n			107			93
Adherence to oral 6-MP						
6-TG metabolite assay, mean (SD)	250.7 (245.3)	283.0 (230.1)	286.5 (307.4)	284.3 (206.4)	302.1 (214.0)	236.8 (148.2)
6MMP metabolite assay, mean (SD)	10 484.6 (9920.6)	11 168.9 (12 107.5)	8499.1 (7600.3)	9218.0 (11 004.2)	10 349.9 (11 667.1)	8087.0 (9123.6)
n	28	24	23	26	22	23
Self-efficacy						
Mean (SD)	155.9 (22.3)	158.0 (24.3)	164.1 (23.4)	156.6 (21.3)	157.9 (22.3)	158.8 (23.5)
n	191	172	164	168	148	139
Cancer knowledge						
Mean (SD)	0.59 (0.20)	0.65 (0.20)	0.66 (0.20)	0.60 (0.20)	0.63 (0.20)	0.63 (0.20)
n	191	172	164	168	148	140
Perceived stress						
Mean (SD)	34.4 (7.4)	36.5 (6.6)	38.1 (6.9)	33.1 (6.6)	35.2 (6.8)	35.7 (6.2)
n	191	170	163	168	146	139
Health locus of control						
Internal, mean (SD)	18.9 (6.1)	18.0 (5.9)	17.5 (6.6)	18.6 (5.3)	18.2 (5.8)	17.7 (6.2)
Chance, mean (SD)	20.3 (6.6)	19.1 (6.1)	18.7 (6.8)	20.7 (7.3)	20.0 (6.6)	19.4 (6.9)
Powerful others, mean (SD)	26.4 (4.7)	26.1 (5.1)	25.7 (5.3)	26.5 (4.6)	26.4 (4.6)	26.2 (4.8)
Doctors, mean (SD)	15.2 (2.5)	15.0 (2.8)	14.7 (2.9)	15.4 (2.6)	15.1 (2.8)	15.0 (2.6)
Other people, mean (SD)	11.1 (3.4)	11.2 (3.4)	11.0 (3.7)	11.1 (3.5)	11.4 (3.2)	11.2 (3.3)
n	190	171	164	168	147	139
Quality of life						
PQL (Minor)						
Mean (SD)	64.2 (15.4)	65.5 (15.1)	69.1 (15.1)	62.5 (17.4)	63.5 (17.6)	66.3 (17.3)
n	154	143	119	134	119	102
FACT-G (Adult)						
Mean (SD)	11.3 (2.6)	11.0 (3.2)	12.2 (2.9)	10.7 (2.7)	11.1 (2.1)	11.3 (2.8)
n	32	25	23	31	29	25

[a] 6-TG and 6MMP units of measurement are pmol/8 × 10^8 red blood cells.

General (for participants ≥18 years of age) did not show a significant group × time interaction in primary intention-to-treat analyses (Pediatric Quality of Life, $P = .112$; Functional Assessment of Cancer Therapy–General, $P = .15$). Intervention and control groups also did not differ significantly in the trajectory of scores of self-perceived stress (Perceived Stress Scale) or health locus of control (Multidimensional Health Locus of Control Scale Form) over time (group × time interaction; Perceived Stress Scale, $P = .931$; Multidimensional Health Locus of Control Scale Form, $P = .608$).

Potential Confounders

To determine whether intervention effects varied as a function of gender or ethnicity or country of residence, we analyzed (1) gender × condition × time, (2) ethnicity × condition × time, and (3) country of residence × condition × time interactions. Results generally failed to identify any differential impact as a function of gender, ethnicity, or country of residence. The sole exceptions involved MEMS-cap–measured TMP/SMX use, in which (1) female participants showed a significantly greater positive effect of the intervention than male participants (gender × condition interaction, $P = .028$), and (2) patients in Australia showed the strongest intervention effects, those in the United States showed intermediate effects, and those in Canada showed the weakest effects (country × condition interaction, $P < .0001$). Intervention effects on TMP/SMX use did not differ as a function of race or ethnicity.

Mediation Analyses

Mediation analyses revealed that changes in cancer-related knowledge from baseline to the average value at 1 and 3 months of follow-up did not fully account for the effects of intervention condition on TMP/SMX adherence (intervention effect: $P = .0357$ controlling for cancer knowledge). Similarly, changes in self-efficacy alone

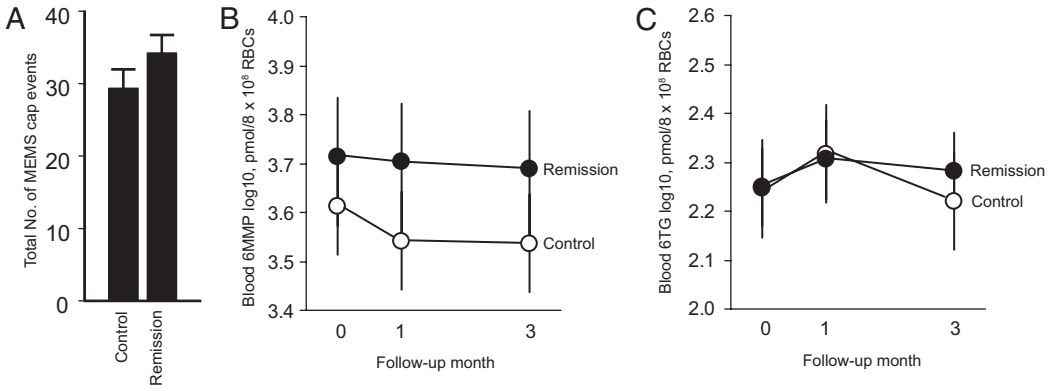

FIGURE 2
Oral medication prescription adherence as measured by frequency (transformed) of TMP/SMX vial cap openings (MEMS) (A) and red cell 6MMP (B) and 6-TG (C) levels according to study group.

did not account for intervention effects on TMP/SMX adherence (intervention effect: $P = .0415$ controlling for self-efficacy in the model); however, analyses that tested self-efficacy and cancer knowledge as joint mediators indicated that these factors together were sufficient to account for all significant effects of intervention condition on TMP/SMX adherence (residual intervention effect $P = .2384$, controlling for both self-efficacy and knowledge). Parallel mediation analyses on 6-MP adherence involving self-efficacy, knowledge, or both variables simultaneously did not account for intervention effects (ie, after controlling for change over time in those variables, intervention condition patients continued to show significantly more favorable trends over time in 6MMP metabolite levels alone, the sum of 6MMP and 6-TG levels, and a repeated-measures analysis that considered 6MMP and 6-TG as separate indicators).

Intervention Adherence Analyses

Given that only 28% of participants fully adhered to the requested 1 hour of game play per week, we sought to determine whether game-play adherence influenced the magnitude of intervention effects on medication adherence. Analysis of MEMS-cap data and 6-MP chemotherapy metabolite levels found similarly strong intervention effects for both those who played less than the requested 12 hours during the 3-month study duration and those who played more (ie, computer adherence × group interaction for TMP/SMX, $P = .12$; and computer adherence × group × time interaction term for simultaneous analysis of 6MMP and 6-TG levels, $P = .62$). Similar findings emerged when analyses distinguished between those who played their assigned game <50% of the requested amount (ie, <6 hours during the course of the entire study). Results continued to indicate a significant beneficial effect of the intervention despite suboptimal game use (6-MP metabolites: group × time interaction, $P = .024$; TMP/SMX use: group effect, $P = .005$).

Adverse Events

One study participant reported a trial-related adverse event. A member of the control group complained of dizziness only while playing the control game. No physiologic causes were found for the dizziness (eg, fluid behind the ears). The patient was withdrawn from the study.

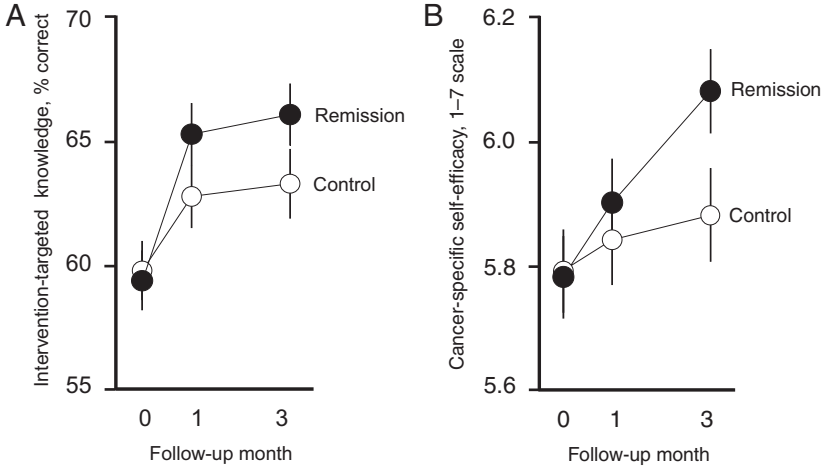

FIGURE 3
Mean (transformed) cancer-related knowledge (A) and self-efficacy scores (B) at baseline and follow-ups according to study group.

DISCUSSION

Results from this multicenter, randomized trial suggest that a behaviorally targeted video-game intervention can enhance adherence to prescribed oral medication regimens in AYA with cancer. These improvements in adherence to therapy are clinically relevant because patients who have cancer and are adherent to oral antibiotic prophylactic regimens have a lower incidence of fevers and infections[13,72] and increased survival,[5] and those who adhere to oral 6-MP chemotherapy regimens show improved survival outcomes.[12,16] The results from this study also showed increases in self-efficacy and cancer-related knowledge among patients who were randomly assigned to the intervention, and these changes may contribute to the intervention's effects on the primary end point of adherence. Self-efficacy and knowledge together were also shown to mediate improvements that were observed in patient adherence to TMP/SMX (although not to 6-MP). Taken together, the findings in this study indicate that an easily distributed video-game–based intervention can have a positive impact on treatment-relevant behaviors and outcomes in a patient population with a serious life-threatening illness.

The interactive game-based intervention that was evaluated in this study represents a novel approach for optimizing patient behavioral participation in cancer treatment regimens. Additional research is needed to define the specific psychological mechanisms by which this game-based approach affects health behaviors; however, consistent with social learning theory,[62] these results suggest that changes in cancer-specific self-efficacy and knowledge about cancer contribute to treatment adherence, specifically to the oral antibiotic TMP/SMX. Several other psychological factors were not significantly altered by this intervention (eg, stress, quality of life, perceived control over health). This pattern of results is consistent with previous studies that highlighted self-efficacy as particularly sensitive to video-game–based intervention.[27] Additional research will also be required to evaluate the scope of behavioral processes that are amenable to change through game-based interventions. This research should also investigate why self-efficacy and knowledge mediated adherence to TMP/SMX but not to oral 6-MP chemotherapy, with a focus on determining whether factors that were not measured in this study, such as anxiety, might have mediated intervention effects on this outcome. Also, the impact of improved adherence to prophylactic antibiotics in the intervention group (approximately one third of doses missed versus one half in the control group) should be investigated further to clarify how much this statistical improvement improves morbidity outcomes and survival rates in this population.

This intervention specifically targeted self-administered oral medication adherence as a component of game play. Self-administered antibiotics and chemotherapy may be particularly amenable to patient-targeted behavioral intervention, and it is unclear whether game-based approaches might affect other behavioral components of cancer treatment. For example, self-report measures of general treatment adherence and clinician-reported attendance at scheduled outpatient clinic visits were not significantly enhanced by this intervention; however, both of those measures were very high at baseline, suggesting that there was little room for improvement. Finally, the absolute lack of adverse effects that were associated with playing the intervention game suggests that it is safe for dissemination to a patient population.

Strengths of this study include the use of a randomized, controlled trial design; a relatively large sample size; a multimodal approach to assessing outcomes (self-report and objective measures); and broad representation of ethnic minority groups in the study population. Limitations include the heterogeneity of cancer diagnoses and treatment regimens and the nonuniform trial entry at varying treatment stages. Although this heterogeneity may reduce statistical power, it may improve generalizability of the findings for application in a broad array of AYA patients with cancer. Direct measures of adherence to TMP/SMX and oral 6-MP were obtained from the subset of the sample who were prescribed these medications, thus making it impossible to determine whether patients who are prescribed other medications would show similar patterns of adherence to their medications if exposed to the intervention game. Male patients were overrepresented among study participants, perhaps because of greater appeal of video games to that audience; however, intervention effects were similar for both genders but with a somewhat greater impact on oral TMP/SMX adherence for female patients. A final limitation involves suboptimal adherence to the video-game intervention, which was used less than the requested amount by most participants in this study. Despite this, there were significant positive effects of Re-Mission even for participants who played the game $<50\%$ of the requested duration. This suggests that shorter durations of play could be recommended during dissemination of the game, which could make this intervention more appealing to patients with a high treatment burden. Some groups demonstrated particularly low game-play rates (eg, African American patients), suggesting that targeted improvements may need to be made to increase the appeal of the game in certain subgroups. Finally, generalizability of the findings may be somewhat limited because access to personal computers that are needed to play the game(s) were provided as part of the study and may not reflect patient access to similar technology in the "real world." Thus, implementation of this intervention should include efforts to ensure that the necessary computer resources are available.

CONCLUSIONS

This study provides preliminary empirical support for the efficacy of a video-game intervention in improving behavioral outcomes in AYA with cancer. Given the role of behavioral factors in influencing chronic disease management more broadly, similar approaches could potentially be directed toward a variety of chronic diseases as an easily distributable approach to improving behavioral disease management. As such, video-game–based inter-

ventions may constitute one component of a broader integrative approach to health care that synergistically combines rationally targeted biological and behavioral interventions to aid patients in the prevention, detection, treatment, and recovery from disease. More broadly, the current results suggest that a carefully designed video game can have a positive impact on health behavior in young people with chronic illness.

ACKNOWLEDGMENTS

This research was supported by HopeLab Foundation, a nonprofit organization. The study sponsor was involved in the study design, collection, analysis, and interpretation of data, writing of the article, and decision to submit it for publication. Per contractual arrangement, the manuscript was submitted to HopeLab before submission. Dr Pollock was supported by grants CA95861, CA098543, and CA054174 from the National Cancer Institute, National Institutes of Health.

We thank the patients who participated in this study and the following people who made this research possible: principal investigators at the study sites: Norma Auger, RN, Med, Jerry Barbosa, MD, Ronald Barr, MD, Anne-Sophie Carret, MD, Gary Dahl, MD, Brian Delaney, PsyD, Janet Franklin, MD, MPH, David R. Freyer, DO, Jami Frost, MD, Jacqueline Halton, MD, Robert J. Hayashi, MD, John Heath, MD, PhD, Maxine Hetherington, MD, Martina Hum, MD, Caroline Laverdiere, MD, Sharon Lockhart, MD, Karen McKinley, PsyD, LCSW, Judith Mullins, MD, Jeffrey Murray, MD, Janice Faye Olson, MD, MHA, Brad H. Pollock, MPH, PhD, O. J. Sahler, MD, Emad Salman, MD, Yvan Samson, MD, Eric Sandler, MD, Judith K. Sato, MD, Hadi Sawaf, MD, Susan Sencer, MD, Linda Stork, MD, Cameron Tebbi, MD, Lilibeth Torno, MD, Raj Warrier, MD, and Robert Wilkinson, MD; site associates: Sandy Baggott, Tina Baggott, RN, PNP, Carolyn Bell, RN, CCRP, CPON, France Bouchard, BSN, Joan Caskey, RN, CCRC, Cercre Church, Sonia Corona-Chico, CCRP, Nancy Eisenberg, Dianne Fochtman, RN, MN, CPNP, D'Arcy Gaisser, RN, Laura Gates, RN, CCRC, Jamie Gender, RN, BSN, CPON, Frances Hamblin, RN, CCRP, Andrea Harvey, MS, MT, CCRC, Jeanne Harvey, APRN, PNP, Kelly Henderson, RN, Julie Hicks, APRN, BC, CPON, Cathy Houde, RN, BSCN, Sally Jones, MA, CCRP, Mary Kessel, Kris Laurence, BHS, CCRP, Margaret Lewis, RN, CCRP, Amanda Matti, RN, BSN, CCRC, Colleen McCarthy, RN, MSN, Patty McCollum, Jill Meredith, BSN, RN, OCN, Kathrynn Mosley, BS, CIP, Kim Nagel, RN, CCRA, Pamela Neu, Emily Place, Louise Renaud, CCRP, Pamela Rennpage, Jessica Sanderson, Tammy Smallwood, Meredith Stockman, Norita Trottier, CCRP, Stacy Truta, David Van Hoff, RN, Gretchen Williams, and Audra Wilson; research project director: Verónica M. Marín-Bowling, Lic; administrative and research support: Nicole Guthrie, MS, Lalita K. Suzuki, PhD, Candice W. Lee, and Robin Avant; other administrative support: Patty Cullen and C. Konditorei; and manuscript review: W. Archie Bleyer, MD, Ronnie D. Barr, MD, and James Sabry, MD, PhD.

Dr Kato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Drs Kato, Cole, Pollock, and Bradlyn were involved in study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and administrative, technical, or material support; Dr Kato was responsible for acquisition of data and obtaining funding; Drs Cole and Pollock were responsible for statistical analysis; and Drs Kato and Pollock were responsible for study supervision.

REFERENCES

1. Bloom BS. Daily regimen and compliance with treatment. *BMJ.* 2001;323(7314):647
2. Tebbi CK, Cummings KM, Zevon MA, Smith L, Richards M, Mallon J. Compliance of pediatric and adolescent cancer patients. *Cancer.* 1986;58(5):1179–1184
3. Smith SD, Rosen D, Trueworthy RC, Lowman JT. A reliable method for evaluating drug compliance in children with cancer. *Cancer.* 1979;43(1):169–173
4. Jamison RN, Lewis S, Burish TG. Cooperation with treatment in adolescent cancer patients. *J Adolesc Health Care.* 1986;7(3):162–167
5. Kennard BD, Stewart SM, Olvera R, et al. Nonadherence in adolescent oncology patients: preliminary data on psychological risk factors and relationships to outcome. *J Clin Psychol Med Settings.* 2004;11(1):30–39
6. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst.* 2002;94(9):652–661
7. Tebbi CK. Treatment compliance in childhood and adolescence. *Cancer.* 1993;71(10 Suppl):3441–3449
8. Albritton K, Bleyer WA. The management of cancer in the older adolescent. *Eur J Cancer.* 2003;39(18):2584–2599
9. Bleyer WA. Cancer in older adolescents and young adults: epidemiology, diagnosis, treatment, survival, and importance of clinical trials. *Med Pediatr Oncol.* 2002;38(1):1–10
10. Lennard L, Lilleyman JS. Variable mercaptopurine metabolism and treatment outcome in childhood lymphoblastic leukemia. *J Clin Oncol.* 1989;7(12):1816–1823
11. Lennard L, Welch J, Lilleyman JS. Intracellular metabolites of mercaptopurine in children with lymphoblastic leukaemia: a possible indicator of non-compliance? *Br J Cancer.* 1995;72(4):1004–1006
12. Schmiegelow K, Schroder H, Gustafsson G, et al. Risk of relapse in childhood acute lymphoblastic leukemia is related to RBC methotrexate and mercaptopurine metabolites during maintenance chemotherapy. Nordic Society for Pediatric Hematology and Oncology. *J Clin Oncol.* 1995;13(2):345–351
13. Festa RS, Tamaroff MH, Chasalow F, Lanzkowsky P. Therapeutic adherence to oral medication regimens by adolescents with cancer: I—laboratory assessment. *J Pediatr.* 1992;120(5):807–811
14. Simone JV. History of the treatment of childhood ALL: a paradigm for cancer cure. *Best Pract Res Clin Haematol.* 2006;19(2):353–359
15. Levine AM, Richardson JL, Marks G, et al. Compliance with oral drug therapy in patients with hematologic malignancy. *J Clin Oncol.* 1987;5(9):1469–1476
16. Richardson JL, Shelton DR, Krailo M, Levine AM. The effect of compliance with treatment on survival among patients with hematologic malignancies. *J Clin Oncol.* 1990;8(2):356–364
17. Dodd MJ. Cancer patients' knowledge of chemotherapy: assessment and informational interventions. *Oncol Nurs Forum.* 1982;9(3):39–44

18. Dodd MJ. Measuring informational intervention for chemotherapy knowledge and self-care behavior. *Res Nurs Health.* 1984;7(1):43–50
19. Blotcky AD, Cohen DG, Conatser C, Klopovich P. Psychosocial characteristics of adolescents who refuse cancer treatment. *J Consult Clin Psychol.* 1985;53(5):729–731
20. Jamison RN, Lewis S, Burish T. Psychological impact of cancer on adolescents: self-image, locus of control, perception of illness and knowledge of cancer. *J Chronic Dis.* 1986;39(8): 609–617
21. Syrjälä AM, Ylostalo P, Niskanen MC, Knuuttila ML. Relation of different measures of psychological characteristics to oral health habits, diabetes adherence and related clinical variables among diabetic patients. *Eur J Oral Sci.* 2004;112(2):109–114
22. Johnson MO, Catz SL, Remien RH, et al. Theory-guided, empirically supported avenues for intervention on HIV medication nonadherence: findings from the Healthy Living Project. *AIDS Patient Care STDS.* 2003;17(12):645–656
23. Fraser C, Hadjimichael O, Vollmer T. Predictors of adherence to glatiramer acetate therapy in individuals with self-reported progressive forms of multiple sclerosis. *J Neurosci Nurs.* 2003; 35(3):163–170
24. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG Adherence Instruments. *AIDS Care.* 2000;12(3):255–266
25. Sietsema JM, Nelson DL, Mulder RM, Mervau-Scheidel D, White BE. The use of a game to promote arm reach in persons with traumatic brain injury. *Am J Occup Ther.* 1993;47(1): 19–24
26. Thomas R, Cahill J, Santilli L. Using an interactive computer game to increase skill and self-efficacy regarding safer sex negotiation: field test results. *Health Educ Behav.* 1997;24(1): 71–86
27. Lieberman DA. Interactive video games for health promotion: effects on knowledge, self-efficacy, social support, and health. In: *Health Promotion and Interactive Technology: Theoretical Applications and Future Directions.* Mahwah, NJ: Lawrence Erlbaum; 1997:103–120
28. Griffiths M. Video games and health. *BMJ.* 2005;331(7509): 122–123
29. Krishna S, Francisco BD, Balas EA, Konig P, Graff GR, Madsen RW. Internet-enabled interactive multimedia asthma education program: a randomized trial. *Pediatrics.* 2003;111(3): 503–510
30. Lieberman DA. Management of chronic pediatric diseases with interactive health games: theory and research findings. *J Ambul Care Manage.* 2001;24(1):26–38
31. Horan PP, Yarborough MC, Besigel G, Carlson DR. Computer-assisted self-control of diabetes by adolescents. *Diabetes Educ.* 1990;16(3):205–211
32. Bandura A. *Social Foundations of Thought and Action: A Social Cognitive Theory*. Upper Saddle River, NJ: Prentice Hall; 1986
33. Brown SJ, Lieberman DA, Germeny BA, Fan YC, Wilson DM, Pasta DJ. Educational video game for juvenile diabetes: results of a controlled trial. *Med Inform (Lond).* 1997;22(1):77–89
34. Davis MA, Quittner AL, Stack CM, Yang MC. Controlled evaluation of the STARBRIGHT CDROM program for children and adolescents with Cystic Fibrosis. *J Pediatr Psychol.* 2004;29(4): 259–267
35. Make-A-Wish Foundation. Ben's Game. Available at: www.wish.org/stories/animals/toys/ben_cancer_videogame. Accessed June 18, 2008
36. Royal Marsden Foundation Trust. The Adventures of Captain Chemo and Chemo Command by Ben de Garis. Available at: www.royalmarsden.org/captchemo/index.asp. Accessed June 18, 2008
37. Horan PP, Yarborough MC, Besigel G, Carlson DR. Computer-assisted self-control of diabetes by adolescents. *Diabetes Educ.* 1990;(16):205–211
38. Cameron LD, Leventhal H. Vulnerability beliefs, symptom experiences, and the processing of health threat information: a self-regulatory perspective. *J Appl Soc Psychol.* 1995;25(21): 1859–1883
39. Leventhal H, Leventhal EA, Contrada RJ. Self-regulation, health, and behavior: a perceptual-cognitive approach. *Psychol Health.* 1998;13:717–733
40. Leventhal H, Brissette I, Leventhal EA. The common-sense model of self-regulation of health and illness. In: Cameron LD, Leventhal H, eds. *The Self-relation of Health and Illness Behavior*. New York, NY: Routledge; 2003:42–65
41. Leventhal H, Diefenbach M, Leventhal EA. Illness cognition: using common sense to understand treatment adherence and affect cognition interactions. *Cognit Ther Res.* 1992;16(2): 143–163
42. Leventhal H. Theories of compliance, and turning necessities into preferences: application to adolescent health action. In: Krasnegor NA, Epstein LH, eds. *Developmental Aspects of Health Compliance Behavior*. Hillsdale, NJ: Lawrence Erlbaum; 1993: 91–124
43. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev.* 1977;84(2):191–215
44. Choi J, Hannafin MJ. Situated cognition and learning environments: roles, structures, and implications for design. *Educ Technol Res Dev.* 1995;43(2):53–69
45. Ellis LB, Raines JR, Hakanson N. Health education using microcomputers: II—one year in the clinic. *Prev Med.* 1982; 11(2):212–224
46. Kulik C, Kulik J. Effectiveness of computer-based instruction: an updated analysis. *Comput Hum Behav.* 1991;7(1–2):75–94
47. HopeLab, TRI, Realtime Associates. *Re-Mission*. Palo Alto, CA: HopeLab; 2004. Available at: www.re-mission.net/site/game/index.php. Accessed June 16, 2008
48. Beale IL, Bradlyn AS, Kato PM. Psychoeducational interventions with pediatric cancer patients: Part II. Effects of information and skills training on health-related outcomes. *J Child Fam Stud.* 2003;12(4):385–397
49. Bradlyn AS, Kato PM, Beale IL, Cole S. Pediatric oncology professionals' perceptions of information needs of adolescent patients with cancer. *J Pediatr Oncol Nurs.* 2004;21(6):335–342
50. Kato PM, Beale IL. Factors affecting acceptability to young cancer patients of a psychoeducational video game about cancer. *J Pediatr Oncol Nurs.* 2006;23(5):269–275
51. Beale IL. Scholarly literature review: efficacy of psychological interventions for pediatric chronic illnesses. *J Pediatr Psychol.* 2006;31(5):437–451
52. Baggott C, Beale IL, Dodd MJ, Kato PM. A survey of self-care and dependent-care advice given by pediatric oncology nurses. *J Pediatr Oncol Nurs.* 2004;21(4):214–222
53. Suzuki LK, Kato PM. Psychosocial support for patients in pediatric oncology: the influences of parents, schools, peers, and technology. *J Pediatr Oncol Nurs.* 2003;20(4):159–174
54. Beale IL. An evaluation model for psychoeducational interventions using interactive multimedia. *Cyberpsychol Behav.* 2002; 5(6):565–580
55. The Collective. *Indiana Jones and the Emperor's Tomb (for Windows)* [computer game]. San Francisco, CA: LucasArts; 2003
56. van de Vijver F, Hambleton RK. Translating tests: some practical guidelines. *Eur Psychol.* 1996;1(2):89–99
57. Kyngas HA, Skaar-Chandler CA, Duffy ME. The development of an instrument to measure the compliance of adolescents with a chronic disease. *J Adv Nurs.* 2000;32(6):1499–1506
58. Morisky DE, Green LW, Levine DM. Concurrent and predictive

validity of a self-reported measure of medication adherence. *Med Care.* 1986;24(1):67–74
59. Waterhouse DM, Calzone KA, Mele C, Brenner DE. Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. *J Clin Oncol.* 1993; 11(6):1189–1197
60. Lee JY, Kusek JW, Greene PG, et al. Assessing medication adherence by pill count and electronic monitoring in the African American Study of Kidney Disease and Hypertension (AASK) Pilot Study. *Am J Hypertens.* 1996;9(8):719–725
61. Lennard L, Singleton HJ. High-performance liquid chromatographic assay of the methyl and nucleotide metabolites of 6-mercaptopurine: quantitation of red blood cell 6-thioguanine nucleotide, 6-thioinosinic acid and 6-methylmercaptopurine metabolites in a single sample. *J Chromatogr.* 1992;583(1): 83–90
62. Bandura A. *Self-efficacy: The Exercise of Control*. New York, NY: WH Freeman and Co; 1997
63. Bandura A. Guide for constructing self-efficacy scales (revised). In: Pajares F, ed. *Self-efficacy Beliefs of Adolescents.* Atlanta, GA: Emory University; 2001
64. Bandura A. Guide for constructing self-efficacy scales. In: Caprara G, ed. *The Assessment of Self-efficacy [in Italian]*. Trento, Italy: Erickson; 2001:15–37
65. Eiser C, Vance YH, Horne B, Glaser A, Galvin H. The value of the PedsQLTM in assessing quality of life in survivors of childhood cancer. *Child Care Health Dev.* 2003;29(2):95–102
66. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes.* 2003;1(1):79
67. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol.* 1993;11(3):570–579
68. Wallston KA, Stein MJ, Smith CA. Form C of the MHLC scales: a condition-specific measure of locus of control. *J Pers Assess.* 1994;63(3):534–553
69. Cohen S, Williamson GM. Perceived stress in a probability sample of the United States. In: Spacapan S, Oskamp S, eds. *The Social Psychology of Health*. Newbury Park, CA: Sage; 1988:31–67
70. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol.* 1986;51(6): 1173–1182
71. Harris R. *A Primer of Multivariate Statistics*. 2nd ed. Orlando, FL: Academic Press; 1985
72. Pizzo PA, Robichaud KJ, Edwards BK, Schumaker C, Kramer BS, Johnson A. Oral antibiotic prophylaxis in patients with cancer: a double-blind randomized placebo-controlled trial. *J Pediatr.* 1983;102(1):125–133

A Video Game Improves Behavioral Outcomes in Adolescents and Young Adults With Cancer: A Randomized Trial

Pamela M. Kato, Steve W. Cole, Andrew S. Bradlyn and Brad H. Pollock

Pediatrics 2008;122;e305
DOI: 10.1542/peds.2007-3134

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

A Video Game Improves Behavioral Outcomes in Adolescents and Young Adults With Cancer: A Randomized Trial

Pamela M. Kato, Steve W. Cole, Andrew S. Bradlyn and Brad H. Pollock

Pediatrics 2008;122;e305
DOI: 10.1542/peds.2007-3134