Exercise and Fatigue in Adolescent and Young Adult Survivors of Hodgkin Lymphoma: A Report from the Children's Oncology Group

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Fatigue is a significant problem for adolescent and young adult (AYA) Hodgkin lymphoma (HL) survivors. The relationship between exercise and fatigue is complex. This study explored the trajectory of and the relationship between exercise and fatigue over 36 months post-therapy in a cohort of 103 AYA-aged HL survivors treated on Children's Oncology Group (COG) study AHOD0031. Descriptive statistics and generalized estimating equations were used in this secondary data analysis. Exercise and fatigue improved over time but were unrelated; amount of exercise at end of therapy predicted amount of exercise at 12 ($p=0.02$) and 36 ($p=0.0008$) months post-therapy.

Keywords: Hodgkin lymphoma, survivorship, exercise, fatigue

HODGKIN LYMPHOMA (HL) is the most common malignancy in adolescents aged 15–19 years.¹ During 2000, in the United States alone, approximately 11,300 young adults between the ages of 15 and 24 years were diagnosed with cancer, and 12% of these cases were HL.²

A recent systematic review and meta-analysis suggested that exercise is generally well-tolerated and may improve the health of cancer survivors.³ Exercise positively impacts fatigue, physical, and psychosocial functioning in adult lymphoma survivors^{4–6} and is recommended for improvement of general physical health and possible attenuation of the impact of late effects of disease and treatment in survivors of pediatric cancer.⁷ However, adult survivors of childhood cancer have been shown to be less physically active than national recommendations, their siblings, or population controls.⁸ Fatigue may present a barrier to exercise, yet high exercise frequency has been associated with lower fatigue.⁹ Some sex differences have also been noted; among females, fatigue appears to both interfere with and predict less physical activity,^{10,11} while for males physical activity predicts less fatigue.¹¹

Fatigue exerts an adverse impact on health-related quality of life (HRQOL) both during treatment and into survivorship.¹² Adolescent and young adult (AYA)-aged survivors of pediatric cancer identify fatigue as the symptom with the greatest negative impact on their daily lives and HRQOL.^{13,14} The Childhood Cancer Survivor Study (CCSS) examined the long-term outcomes of pediatric cancer survivors, including their HRQOL. Pediatric HL survivors are included among the 14,000 CCSS active participants who completed a baseline survey.¹⁵ In a follow-up survey of CCSS participants that included more in-depth self-report measurements of fatigue and sleep, CCSS researchers found the cohort of HL survivors reported significantly more fatigue, sleep disturbance, and daytime sleepiness and lower HRQOL in physical function and general health domains compared with siblings.¹⁶

Despite these data, the trajectories of and relationship between exercise and fatigue have not been longitudinally addressed during the initial years of survivorship. This is a critical period during which patients remain relatively accessible to intervention that could improve longer-term

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survivorship outcomes. The aim of this analysis was to explore the trajectories of and relationship between amount of exercise and fatigue from end of therapy through 36 months post-therapy in a cohort of AYA-aged HL survivors treated in the contemporary era of therapy. The research questions were:

RQ1: *What are the patterns of change over time from end of therapy to 12 and 36 months post-therapy in self-reported exercise and fatigue?*

RQ2: *Does the amount of self-reported exercise at end of therapy predict either the amount of self-reported fatigue at end of therapy, or at 12 or 36 months post-therapy, or predict the amount of self-reported exercise at 12 or 36 months post-therapy?*

Methods

Data source

A secondary analysis was conducted on data from a cohort of 103 AYA-aged HL survivors that met the following criteria: (a) diagnosed while aged 13–21 years old; (b) treated on Children's Oncology Group (COG) study AHOD0031; and (c) completed a self-report survey at end of therapy and 12 and 36 months post-therapy, which included items addressing amount of exercise and fatigue. COG AHOD0031 was a phase III randomized clinical trial that evaluated dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate risk HL.¹⁷ All Patients were treated initially with two cycles of multi-agent chemotherapy (ABVE-PC: doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide). After an early response determination, those with a rapid early response went on to receive two additional cycles of the same chemotherapy, whereas those patients who showed a slow early response were randomized to two additional cycles of the same chemotherapy $\pm$ two additional courses of DECA (dexamethasone, etoposide, cytarabine, and cisplatin). At the conclusion of chemotherapy, all slow early responders received low-dose involved-field radiotherapy (IFRT). Rapid early responders were assessed for complete response (CR). Those in CR were then randomized to IFRT or no further therapy. Those not in CR were non-randomly assigned to IFRT.

The treatment study (AHOD0031) included a self-report survey administered at end of therapy, and 12, 36, 60, 84, and 120 months post-therapy. The end of therapy and 12- and 36-month time points had sufficient data to use for this analysis. The survey utilized the baseline questionnaire from the CCSS study and included items assessing demographics, medical history, functional limitations, psychological outcomes, work history, and living circumstances.¹⁵ The functional limitation items addressing amount of exercise and fatigue were the focus of this examination, and were scored in the same manner as in the CCSS (pers. comm. D. L. Friedman and M. Hudson, 2011). Amount of exercise was assessed by asking the number of days (response options 0–7) in a typical week on which the patient exercised or did sports for at least 20 minutes that made him/her sweat or breathe hard (e.g., dancing, jogging, basketball, etc.). Fatigue was assessed by asking whether during the preceding 2 weeks the patient had: felt tired, had trouble finishing tasks because s/he tired quickly, needed to sleep during the day, been frustrated by

being too tired to do things s/he wanted to do, or had to limit his/her social activities because of fatigue. Response options were “not at all,” “a little bit,” “moderately,” “quite a bit,” and “very much so.”

Analysis

Descriptive summaries were produced using means, frequencies, and percentages. Paired *t*-tests were used to compare amount of exercise between end of therapy and 12 months post-therapy and between 12 months post-therapy and 36 months post-therapy. Fatigue scores were reverse coded with 0 = “very much so,” 1 = “quite a bit,” 2 = “moderately,” 3 = “a little bit,” and 4 = “not at all,” so higher scores represent less fatigue. McNemar's test was used to compare fatigue scores between end of therapy and 12 months post-therapy and between 12 months post-therapy and 36 months post-therapy. SAS PROC GENMOD was used to fit generalized estimating equations (GEE)¹⁸ for binary response data of fatigue using a binomial distribution with a logit link function and for count response data of days per week exercised using a Poisson distribution with a log link function. SAS PROC GENMOD accounts for the correlated nature of the data collected at baseline and at 12 and 36 months. The analyses presented in the regression models represent patients with data available for all three time points for this descriptive exploratory study. All analyses were conducted using SAS/STAT software for Windows v9.2.

Results

Table 1 displays demographic, disease, and treatment information for the study cohort. Mean age at diagnosis was 15.46 years (range 13–21 years); 57% were female and 84%

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

	Frequency	Percent
Sex		
Female	59	57.28
Male	44	42.72
Race/ethnicity		
White	87	84.47
Black	9	8.74
Other	5	4.85
Unknown	2	1.94
Stage		
I	7	6.80
II	67	65.05
III	16	15.53
IV	13	12.62
Protocol treatment arm		
Rapid early responders		
ABVE-PC $\times$ 4, <CR, IFRT	47	45.63
ABVE-PC $\times$ 4, CR, IFRT	15	14.56
ABVE-PC $\times$ 4, CR, NO IFRT	26	25.24
Slow early responders		
ABVE-PC $\times$ 4 + IFRT + DECA $\times$ 2	10	9.71
ABVE-PC $\times$ 4 + IFRT	5	4.85
Total cohort <i>N</i>	103	100

ABVE-PC, doxorubicin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide; CR, complete remission; DECA, dexamethasone, etoposide, cytarabine, cisplatin; IFRT, involved-field radiation therapy.

TABLE 2. MEAN DAYS OF EXERCISE PER WEEK REPORTED AT END OF THERAPY AND 12 AND 36 MONTHS POST-THERAPY

<i>End of therapy</i>			<i>12 months post-therapy</i>				<i>36 months post-therapy</i>			
N	M	SD	N	M	SD	p*	N	M	SD	p**
98	2.74	2.17	86	2.70	1.99	0.90	91	2.92	2.16	0.26

*12-month change from baseline, paired *t*-test.

**36-month change from baseline, paired *t*-test.

were white. The majority of patients (65%) had stage II disease, and almost half (46%) were rapid early responders who were treated with ABVE-PC for four cycles and then non-randomly received IFRT, as they were not in complete remission at the end of chemotherapy.

Both amount of exercise and fatigue improved from end of therapy to 36 months post-therapy (Tables 2 and 3), although not significantly ($p \geq 0.05$). Mean days per week of exercise decreased slightly from end of therapy (2.74 days per week) to 12 months post-therapy (2.70 days per week) before increasing at 36 months post-therapy (2.92 days per week).

Using GEE and adjusting for sex, age at diagnosis, stage at diagnosis, and protocol treatment arm, amount of exercise was not predictive of fatigue at end of therapy or at 12 or 36 months post-therapy ($p > 0.05$). However, amount of exercise at end of therapy predicted amount of exercise at both 12 ($p = 0.02$) and 36 ($p = 0.0008$) months post-therapy.

Discussion

The expected but modest improvement of both amount of exercise and fatigue from end of therapy to 36 months may reflect the relatively mild fatigue and moderate amount of exercise at end of therapy baseline. With regard to exercise, it is also possible that during the initial 12 months post-therapy, survivors were focused on other aspects of their recovery, such as re-engaging in educational pursuits or social obligations, and that a renewed focus on exercise (and possibly other health-related behaviors) began later in the trajectory of recovery. Discrepancy between fatigue experience and impact of fatigue upon function and a ceiling effect on fatigue impact has been described.¹⁹ AYAs reported the fatigue experience¹⁹ (feeling tired) as more intense and persistent than the impact of fatigue upon function¹⁹ (trouble finishing tasks, needing to sleep during the day, frustration due to the inability to do what one wants, having to limit social activities).

Despite the decline from end of therapy to 36 months post-therapy, mild fatigue persisted in the study sample. Therefore, improved understanding of fatigue and its impact on young HL survivors is necessary. Exercise during treatment and throughout survivorship may ameliorate fatigue in AYA-aged survivors.¹¹ In the present data, the lack of relationship between amount of exercise and fatigue suggests that exercise may have ameliorated the subjective sensation and/or consequences of fatigue for some AYA-aged HL survivors, while for others exercise may have had no effect or even worsened fatigue. It also raises the possibility that the subjective sensation and/or consequences of fatigue for some AYA-aged HL survivors may not influence the amount of exercise in which they engage; some may persist in exercise despite fatigue, while others may avoid exercise due to fatigue.

Amount of exercise at end of therapy predicting amount of exercise at 12 and 36 months post-therapy supports promoting exercise during therapy to establish it as a habitual behavior, rather than waiting until post-therapy.²⁰ This recommendation is potentially generalizable beyond the HL disease-specific population to all AYAs during therapy and in survivorship.

Limitations

The primary limitation of the data set was measurement of amount of exercise and fatigue by single items rather than by comprehensive instruments with total and subscale scores, reported reliability and validity, and cut scores. This approach may not have fully elicited all relevant domains of the constructs. For example, only vigorous exercise was captured but not light or moderate exercise. This approach does not facilitate interpretation of clinical significance or comparison of study results to those of other studies of AYA-aged survivors or healthy population norms. Measurement solely by self-report is also a notable limitation. However, it was necessary to rely solely on self-report for this analysis, as

TABLE 3. MEAN FATIGUE ITEM SCORES REPORTED AT END OF THERAPY AND 12 AND 36 MONTHS POST-THERAPY

<i>Item</i>	<i>End of therapy</i>			<i>12 months post-therapy</i>				<i>36 months post-therapy</i>			
	N	M	SD	N	M	SD	p*	N	M	SD	p**
Felt tired	97	2.71	1.05	88	2.64	1.22	0.74	94	2.73	1.18	0.74
Had trouble finishing tasks because tired quickly	96	3.33	0.94	87	3.36	0.94	0.99	93	3.46	0.88	0.42
Needed to sleep during the day	97	3.20	0.95	88	3.05	1.21	0.25	94	3.25	0.96	0.20
Frustrated by being too tired to do things he/she wanted to do	97	3.32	1.07	88	3.40	1.13	0.88	93	3.54	0.90	0.47
Needed to limit social activities because of fatigue	96	3.33	1.11	87	3.66	0.68	0.045	94	3.68	0.79	0.82

*12-month change from baseline, paired *t*-test.

**36-month change from baseline, paired *t*-test.

functional performance ratings were not included in the data set.

Recall bias is an ever-present limitation in studies relying on individuals' reports of feelings and behaviors. Self-report bias is also likely given the human tendency to over-report socially desirable behaviors such as amount of exercise and under-report problems that may be perceived as weaknesses such as fatigue. Response bias regarding the representativeness of those who completed the questionnaires at all three time points as compared to those who did not cannot be ruled out, as it is possible that the responders differ in some systematic and non-random manner from the non-responders.

Conclusions

The study finding that amount of exercise at end of therapy predicted amount of exercise at both 12 and 36 months post-therapy in AYA-aged HL survivors provides additional evidence for the importance of promoting exercise from the time of initiation of cancer therapy, not waiting until the transition to survivorship care. Future study is necessary to elucidate the nature of the relationship between fatigue and exercise more precisely and to design and evaluate exercise interventions for AYAs with cancer.

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