Interferon-Induced Fatigue in Patients With Melanoma: A Pilot Study of Exercise and Methylphenidate

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Purpose/Objectives: To examine the effect of exercise and methylphenidate on fatigue, functional ability, and cognitive function in patients with melanoma.

Design: Pilot study with comparison to historic controls.

Setting: University-based cancer center.

Sample: 12 patients with melanoma entered and completed the study. The mean age was 44 years.

Method: Eligible patients were recruited before their first dose of interferon-a (IFN-a). Patients were instructed to take 20 mg sustained-release methylphenidate every morning and follow an aerobic exercise program four days a week for 15–30 minutes. Measures included a 12-minute walk, the Schwartz Cancer Fatigue Scale, Trail Maker Forms A and B, Medical Outcomes Study 36 Short Form, body weight, and daily logs. Fatigue scores were compared to usual care historical controls with melanoma receiving only IFN-a.

Main Research Variables: Fatigue, functional ability, and cognitive function.

Findings: 66% adhered to exercise and methylphenidate; all adhered to exercise. Fatigue was lower for the exercise and methylphenidate group than historic controls. Functional ability increased 6% for all patients and 9% for the exercise and methylphenidate group. Cognitive function was stable for the exercise and methylphenidate group. The exercise-only group showed marked cognitive slowing.

Conclusions: The combination of aerobic exercise and methylphenidate may have a positive effect on fatigue, cognitive function, and functional ability. A larger sample size and randomized trial is needed to more rigorously evaluate the results of exercise and methylphenidate alone or in combination.

Implications for Nursing: Although further study is needed, a combination of exercise and methylphenidate may be a practical intervention for patients receiving IFN-a for melanoma.

Key Points . . .

- Exercise and methylphenidate, either alone or in combination, may reduce interferon-a-induced fatigue.
- Exercise and methylphenidate may lessen the negative impact of interferon-a on cognitive function.
- Although further study is needed, exercise and methylphenidate may be an effective intervention for management of interferon-a-induced fatigue and, thus, may improve tolerance of an effective treatment.

Cancer treatment-related fatigue is a significant problem for the majority of patients with cancer, affecting both physical and cognitive function (Atkinson et al., 2000; Curt et al., 2000). When examining the incidence of fatigue across different types and stages of cancer and treatment, the incidence varies from 40%–100% of patients (Atkinson et al.). Fatigue is a recognized, treatment-limiting side effect of some therapeutic regimens. Interferon-a (IFN-a) is one of the drugs associated with this dose-limiting side effect (Capuron, Ravaud, & Dantzer, 2000). Although the efficacy of high-dose IFN-a (i.e., 10–20 million IU/m^2) in the treatment of melanoma has been demonstrated, the impact of treatment-related fatigue is significant and contributes to reductions in the prescribed dose during both the induction and maintenance phases of therapy (Kirkwood et al., 1996). Even when subjects change from the IV induction phase to the subcutaneous maintenance phase of IFN-a, the effects of fatigue continue to influence patient adherence to IFN-a for the duration of treatment. Although cognitive deficits were not an outcome measure

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Digital Object Identifier: 10.1188/02.ONF.E85-E90

in the Kirkwood et al. study, patients treated with IFN-a have performed poorly on neurobehavioral function tests (Meyers, 1999; Pavol et al., 1995), had a syndrome of mood disturbance with cognitive slowing, and experienced impaired function (Valentine, Meyers, Kling, Richelson, & Hauser, 1998). To improve patient tolerance for high- and moderate-dose (≥ 3 million IU/m^2) IFN-a, interventions are needed that will minimize side effects, improve quality of life, and potentially improve long-term outcomes.

Few interventions for fatigue have been tested formally, although exercise has received some attention. Aerobic exercise has a powerful effect on reducing fatigue and improving quality of life in women with breast cancer receiving adjuvant chemotherapy and in patients following bone marrow transplant. Exercise studies in patients with cancer suggest that aerobic exercise prevents loss in functional capacity and reduces nausea, cognitive problems, fatigue, and other quality-of-life issues (Dimeo, Fletcher, Lange, Mertelsmann, & Keul, 1997; Dimeo, Stieglitz, Novelli-Fischer, Fetscher, & Keul, 1999; Dimeo, Tilmann, et al., 1997; Mock et al., 1994, 1997; Schwartz, 1998, 1999, 2000). The psychostimulant methylphenidate is an alternative pharmacologic intervention for fatigue. Methylphenidate is proposed to reduce fatigue and improve concentration in patients with cancer (National Cancer Institute [NCI], 2000).

Methylphenidate is a drug used to control hyperactivity and attention deficit disorder in children and has been suggested to have a beneficial effect in controlling fatigue, increasing energy, and managing depression in patients with cancer (NCI, 2000). Methylphenidate's mechanism of action is not understood completely but is believed to increase brain stem and cortical arousal to produce its stimulant effect (Novartis Pharmaceuticals, 2001). Methylphenidate is promulgated widely as an effective intervention to reduce fatigue and improve concentration and cognitive function, although no studies document its efficacy in the adjuvant IFN-a therapy setting (NCI). Psychostimulants have been useful for patients with advanced cancer who express depression, diminished concentration, decreased energy, and weakness (Olin & Masand, 1996; Wilwerding et al., 1995). Methylphenidate has demonstrated efficacy in decreasing drowsiness and improving nighttime sleep in patients with cancer receiving strong narcotics (Bruera, Miller, Macmillan, & Kuehn, 1992; Portenoy, 1989; Wilwerding et al.) or with brain tumors (Meyers, Weitzner, Valentine, & Levin, 1998). Methylphenidate also has been shown to improve neurobehavioral functioning in patients with tumor-related organic brain dysfunction (Weitzner, Meyers, & Valentine, 1995). Dose-limiting side effects include elevated heart rate and blood pressure and feelings of nervousness and overstimulation (Novartis Pharmaceuticals). The use of methylphenidate in combination with exercise may prove to have beneficial effects in minimizing the fatigue and cognitive problems associated with IFN-a.

The primary objective of this pilot study was to examine tolerance for treatment, fatigue, functional ability, and cognitive function in patients with melanoma receiving at least five million IU/m^2 of IFN-a three times per week over the first four months of treatment. The secondary aims were to determine the percentage of patients who adhered to IFN-a treatment, methylphenidate, and the exercise regimen. Researchers in the current study hypothesized that patients who adhered to the exercise and pharmacologic intervention would have lower levels of fatigue and improved functional ability and cognitive function.

Methods

Patients

Twelve patients with histologically documented melanoma were entered into the study after consenting to participate. Eligibility criteria included patients who were beginning IFN-a treatment with a dose of at least five million IU/m^2, ambulatory, more than 18 years of age, and able to read and write in English. Patients with uncontrolled hypertension; anxiety disorders; active central nervous system metastasis; hypersensitivity to methylphenidate; a history of glaucoma, motor tics, or seizure disorders; or a family history or diagnosis of Tourette's syndrome were excluded from the study. The exclusion criteria were set to minimize the risk of side effects from methylphenidate. All patients signed a written consent approved by the local institutional review board and were enrolled before their first dose of IFN-a. Sixteen usual care historic controls receiving IFN-a treatment for melanoma enrolled in an instrumentation study were used to compare fatigue patterns between usual care patients and those in this study who adhered to exercise and methylphenidate or only to exercise.

Intervention

Patients were instructed to take 20 mg sustained-release methylphenidate by mouth each morning upon rising. Morning dosing was selected so that the drug would be effective during the day and not interfere with sleep at night. Patients were given a booklet describing an aerobic exercise program to follow four days a week for 15–30 minutes. The duration and intensity of exercise gradually increased over the four months of the study. The exercise intensity was limited by symptoms. Patients were instructed to choose an aerobic activity they enjoyed (e.g., walking, running, cycling), slow down their pace if they experienced increases in fatigue, pain, or other side effects, and stop if the discomfort persisted.

Instruments

All patients were assessed for fatigue, functional ability, cognitive function, and ability to adhere to the exercise intervention. Measures were completed before the first dose of IFN-a.

Table 1. Sample Characteristics

	Pilot Subjects N = 12		Historic Controls N = 16	
Characteristic	**n**	**%**	**n**	**%**
Race				
Caucasian	11	92	16	100
Asian	1	8	–	–
Education				
High school graduate	2	17	8	50
Some college/technical school	2	17	5	31
College graduate	8	66	3	19
Employment status				
Full-time	8	67	13	81
Part-time	1	8	3	19
Retired	3	25	–	–
Stage of disease				
II	2	16	2	12
III	10	84	14	88

Table 2. Changes in Functional Ability Measured in a 12-Minute Walk

	Methylphenidate and Exercise		Exercise Only	
Interval	$\bar{X}$	SD	$\bar{X}$	SD
Baseline	1,143	450	1,046	338
One month	1,175	450	1,094	386
Four months	1,257	467	1,104	161

Note. Distance was measured in meters.

Functional ability was measured using a **12-minute walk.** Patients were asked to walk or run as far and as fast as they could for 12 minutes. The 12-minute walk is a reliable and valid measure that is used commonly to study functional exercise ability in patients with cancer (Cooper, 1968; Larson et al., 1996; Mock et al., 1994, 1997; Schwartz, 1999, 2000). The 12-minute walk is strongly correlated (r = 0.90) with oxygen consumption tested in the laboratory (Bernstein et al., 1994). The 12-minute walk test was conducted at baseline and months one and four.

Daily activity and medication logs were maintained by all subjects for the duration of the study and mailed to the study site at monthly intervals. Information from the logs was used to determine exercise adherence. The logs included information on duration, intensity, frequency, and effort of exercise and inquired about missed doses of methylphenidate.

The **Schwartz Cancer Fatigue Scale,** a brief, six-item scale, is used to measure fatigue on physical and perceptual subscales. Scores for the scale then are summed and range from 6–36. The scale has demonstrated content and constructs validity and reliability. Cronbach's coefficient alpha for the total scale is 0.90 and is 0.88 and 0.81 for the physical and perceptual subscales, respectively (Schwartz, 1998; Schwartz & Meek, 1999). Subjects completed the fatigue scale at monthly intervals.

Cognitive function was measured using **Trail Maker Forms A and B.** Trail Maker is a good measure of general brain function because it requires recognition of numbers and letters, the ability to scan an 8.5" x 11" page to identify the next number or letter, flexible integration of number and alphabetical series, and the ability to complete the test under time pressure. Form A is simpler and requires connecting numbers that are scattered over the page. Form B is more challenging and requires the individual to connect numbers and letters in alphanumeric order. The visual scanning tests the right brain hemisphere, numeric and language symbols test the left brain hemisphere, and adequacy of brain function is tested by the speed and efficiency of completion (Reitan, 1955, 1958). Test-retest reliability has been established in numerous studies (Reitan & Wolfson, 1992), and recent reports (Form A: r = 0.75; Form B: r = 0.85) support the earlier results (Giovagnoli et al., 1996). Scores are determined by time; therefore, the faster an individual completes the tests, the higher his or her cognitive function is. Normal scores on Form A range from 27–39 seconds, and Form B scores range from 66–85 seconds. This measure was obtained at baseline and months one and four.

The **Medical Outcomes Study 36 Short Form** (SF-36) physical functioning and mental health subscales were used as general measures of function. Scores for each of the subscales range from 0–100, with higher scores representing higher levels of functioning. Validity of the SF-36 was determined using data from more than 20,000 patients. The SF-36 was found to be a reliable (α = 0.7–0.9) and valid measure of physical and mental health functioning and has published norms for the general U.S. population (McHorney, Ware, & Raczek, 1993). The SF-36 has been used widely to measure quality of life in patients with cancer during and following treatment (Albertsen, Aaronson, Muller, Keller, & Ware, 1997). Physical and mental function are considered a reflection of a patient's quality of life; quality of life generally is described as multidimensional. The physical and mental dimensions of quality of life are aspects that patients commonly say are related to reduced quality of life. This measure was obtained at baseline and months one and four.

Body weight was measured to the nearest 0.1 kg and obtained at monthly intervals. Researchers followed up by telephone at regular intervals (i.e., one week, two weeks, four weeks, and monthly thereafter) to improve compliance with exercise, address barriers to exercise, determine methylphenidate side effects, and assess compliance with the regimen.

Data Analyses

Descriptive analyses were used to describe the sample and each measure. Patients were defined as adhering to the exercise intervention if they reported exercising at least four days per week in their exercise logs. Patients were assumed to have taken methylphenidate if they reported doing so in their logs and returned to the clinic for refills. Correlations were examined between percent change in the 12-minute walk from baseline to post-test and fatigue and cognitive function. Fatigue levels of patients in this trial were compared to 16 usual care historic control patients with melanoma receiving IFN-α. This data was obtained in a multisite fatigue instrumentation study (Schwartz, 1997).

Results

Patient Characteristics

The clinical characteristics of the 12 patients who participated in this pilot study and the historic controls are presented in Table 1. Mean age was 44 years (range = 20–64). Eighty-four percent of patients had stage III disease. All were newly diagnosed and had undergone surgery but had not received prior adjuvant therapy for melanoma. Only two patients exercised regularly at study entry.

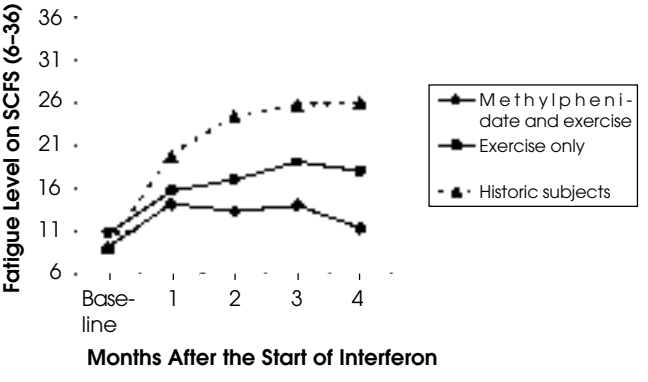

Figure 1. Pattern of Fatigue

SCFS—Schwartz Cancer Fatigue Scale

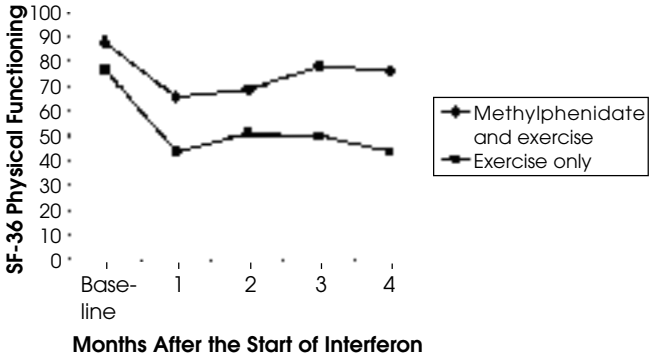

Figure 2. Physical Functioning Subscale Scores on the Medical Outcomes Study 36 Short Form

SF-36—Medical Outcomes Study 36 Short Form

Treatment

All patients (N = 12) exercised for four months, and eight patients also took methylphenidate. Three patients (25%) voluntarily discontinued methylphenidate within 48 hours of beginning the drug. One patient complained of indigestion, another complained of mild nervousness, and one chose to stop taking the methylphenidate because she was taking too many medications. A fourth patient returned for a follow-up appointment after one week with marked anxiety and was withdrawn from the methylphenidate. Although 33% of the sample stopped taking methylphenidate within the first week of the study, only one of the four patients appeared to experience side effects from the medication. The remaining eight subjects took the methylphenidate throughout the study. The four patients who stopped taking the methylphenidate but continued to exercise remained in the study as an exercise-only group.

Exercise adherence was remarkable in this sample. All patients (N = 12) reported exercising at least four days a week for at least 15 minutes in their exercise logs, and all demonstrated improvements in their functional ability.

Functional Ability

Functional ability increased an average of 6% for all subjects (see Table 2). Greater improvements in functional ability were observed in the patients who also took methylphenidate ($\overline{X}$ = 9%). Because the sample was small, no statistical differences were observed in functional ability between those who took and those who did not take methylphenidate.

Fatigue

Fatigue scores on the Schwartz Cancer Fatigue Scale demonstrated modest increases over the course of four months. When fatigue scores of usual care historic controls were compared to results from this sample, exercise alone may have reduced fatigue and the combination of exercise and methylphenidate may have had a striking effect on the pattern of fatigue over time (see Figure 1). The effect of exercise and perhaps methylphenidate reduced fatigue scores and changed the daily pattern of fatigue to be more regular and less chaotic (Schwartz, 2000) for all patients in this pilot study compared to the historic control patients. Although percent change on the 12-minute walk from baseline to post-test was not significantly correlated with fatigue scores of patients (r = –0.30, p = 0.56), the inverse correlation was in the expected direction (i.e., the more patients exercised, the lower their levels of fatigue would be).

Cognitive Function

Cognitive function scores were normal for all subjects on Trail Maker Form A. Subjects who took methylphenidate maintained a stable level of function (baseline = 30.5 seconds, four months = 31.3 seconds), whereas the exercise-only group declined in cognitive function from a mean at baseline of 23 seconds to 28 seconds at four months. Increasing time to completion of the Trail Maker Forms indicates declining cognitive function.

The majority of subjects' scores were in the normal range (i.e., 66–85 seconds) on Trail Maker Form B. At baseline, the methylphenidate group's mean score was 67.1 seconds and 69.8 seconds at four months. However, a decline in cognitive function was identified among the exercise-only group (baseline $\overline{X}$ = 72.6 seconds, four months $\overline{X}$ = 82.6 seconds). The 82.6-second score at the four-month interval is considered borderline impaired. Two of the exercise-only subjects' scores suggested mild to moderate cognitive impairment. These patients' scores exceeded 86 seconds on Trail Maker Form B. An inverse correlation was identified between percent change in the 12-minute walk and scores on Trail Maker Forms A (r = –0.64, p = 0.04) and B (r = –0.67, p = 0.05), which suggests a possible relationship between higher levels of exercise and improved cognitive function (i.e., lower scores on Trail Maker). Taking methylphenidate was correlated with improved performance on Trail Maker Form B at four months (r = –0.85, p < 0.001).

Physical and Mental Function

All subjects taking methylphenidate reported that they continued to work and maintain their usual activities over the study period. This contrasts the exercise-only group that unanimously reported disruptions in their activity and work patterns.

Scores on the physical functioning subscale of the SF-36 ranged from a high at baseline (methylphenidate group $\overline{X}$ = 87.5, exercise-only group $\overline{X}$ = 76.6) to a low at the end of four months (methylphenidate group $\overline{X}$ = 76.7, exercise-only group $\overline{X}$ = 43.7). The scores for those who took methylphenidate declined by 12.4%, whereas the scores for the exercise-only participants declined by 43%. The level of physical functioning for the exercise-only group was lower at baseline and

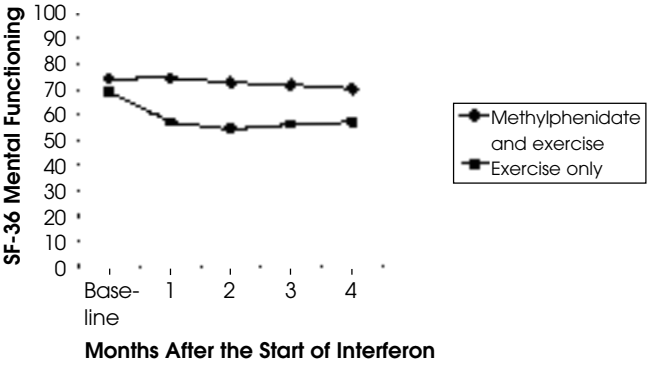

Figure 3. Mental Health Subscale Scores on the Medical Outcomes Study 36 Short Form

SF-36—Medical Outcomes Study 36 Short Form

Table 3. Differences in Body Weight in Kilograms Between the Methylphenidate and Exercise Group[a] and the Exercise-Only Group[b]

	Methylphenidate and Exercise		Exercise Only			
Interval	$\bar{X}$	SD	$\bar{X}$	SD	t	p
Baseline	87.2	17.5	85	17.8	0.185	0.86
One month	85.5	16.5	78.5	19.5	0.600	0.56
Four month	79.1	15.2	76.8	17.7	0.396	0.70

[a] N = 8
[b] N = 4

continued to demonstrate declines in physical functioning over time. In contrast, those taking methylphenidate demonstrated some improved functional ability at months two through four (see Figure 2). Mental health scores also differed for the two groups at baseline (methylphenidate group $\bar{X}$ = 74, exercise-only group $\bar{X}$ = 69). However, both groups showed a gradual decline in mental health over time with four-month mean scores of 70 for the methylphenidate group (6% decline) and 58 for the exercise-only group (16% decline) (see Figure 3).

Body Weight

Both groups lost weight over the four months: Those who took methylphenidate, on average, lost 8.1 kg, and the exercise-only group, on average, lost 8.2 kg (see Table 3). The weight loss observed was consistent with the degree of weight loss commonly noted in patients receiving comparable doses of IFN-a.

Discussion

This pilot study was designed in an attempt to improve tolerance to IFN-a treatment. Because of the small sample size and nonrandomized design, the results need to be interpreted with caution. Although fatigue is recognized as a severe and dose-limiting side effect of IFN-a therapy, the combination of exercise and methylphenidate appears to have a positive effect on functional ability, fatigue, and cognition. Exercise has a strong effect on reducing fatigue in patients with breast cancer and patients receiving peripheral stem cell transplants (Dimeo, Fletcher, et al., 1997; Dimeo, Tilmann, et al., 1997; Mock, 1994, 1997; Schwartz, 1998, 1999, 2000). In this small sample, exercise appeared to reduce fatigue and have a positive effect on cognitive function. For the few patients who did not take methylphenidate, exercise may have contributed to lower levels of fatigue than were reported in historic controls. Methylphenidate may have a positive effect on exercise adherence, which may influence other variables, such as functional ability, fatigue, cognitive function, and perhaps even overall tolerance for treatment. However, a larger sample size and randomized trial is needed to determine the effects of exercise and methylphenidate alone and in combination.

Methylphenidate is recommended for reducing fatigue and improving concentration and attention. Similar to findings of patients with organic brain dysfunction (Weitzner et al., 1995), methylphenidate in the current study's sample appeared to help patients maintain relatively stable cognitive function. Changes in attention and cognitive function have not been reported previously in patients with melanoma receiving IFN-a, so it is not possible to speculate to what extent exercise or methylphenidate may have affected physical or mental functioning.

Cognitive dysfunction is recognized as a serious side effect of therapy that affects memory and ability to work (van Dam et al., 1998). Negative effects of IFN-a therapy have been noted in patients with leukemia who perform below expectations on neurobehavioral tests (Pavol et al., 1995). With the exception of a few studies about attentional fatigue (Cimprich, 1992, 1998, 1999) and small studies of neurobehavioral deficits (Meyers & Weitzner, 1995; Pavol et al.), little research has been conducted to examine changes in attention and cognitive function. However, exercise and methylphenidate may alleviate some of the psychomotor retardation associated with IFN-a therapy in patients with melanoma. Measuring levels of depression may have added insight into the relationship among cognitive dysfunction, fatigue, and depression.

Although the results of this pilot study are intriguing, significant limitations exist that only can be addressed with a randomized trial to rigorously evaluate the efficacy of exercise and methylphenidate, alone and in combination, on side effect frequency and intensity and tolerance for treatment. The limitations of this study include its small sample size, lack of randomization, and lack of depression measure. Future studies should consider a methylphenidate regimen with provisions for dose escalation and reduction and a lower starting dose of methylphenidate (e.g., 10 mg daily) to reduce the drug's side effect profile. In addition, interesting clinical evidence supports the examination of selective serotonin reuptake inhibitors (SSRIs) in the management of fatigue and depression associated with IFN-a therapy. SSRIs, such as Effexor® (venlafaxine, Wyeth-Ayerst, Philadelphia, PA), may reduce fatigue by acting on both norepinephrine and serotonin reuptake and enhancing serotonin neurotransmission (Stahl, 1998). The information gained from future neurobehavioral and quality-of-life studies may improve the functioning of patients during treatment and, ultimately, affect survivorship.

The authors gratefully thank Lillian Nail, PhD, RN, FAAN, for her thoughtful review and critique and Integrated Therapeutics Group/ Schering Pharmaceuticals, Inc., for unrestricted educational support of this work.

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For more information . . .

- ➤ CancerFatigue.org
  www.cancerfatigue.org
- ➤ Cancer Survivors Network: Long-Term Fatigue With Interferon
  www.acscsn.org/global/pdfs/722.pdf
- ➤ Hepatitis Council: Fatigue Facts
  www.hepccouncilsa.asn.au/fatigue.html

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