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Acupuncture for Postchemotherapy Fatigue: A Phase II Study

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ABSTRACT

Purpose
To determine whether improvement in postchemotherapy fatigue following acupuncture treatment is substantial enough to warrant a controlled trial.

Patients and Methods
We accrued patients at Memorial Sloan-Kettering Cancer Center who had completed cytotoxic chemotherapy but experienced persisting fatigue. Patients with severe anemia, clinical depression, or Karnofsky performance status score less than 70 were excluded. Thirty-seven patients were registered in two cohorts; 31 provided follow-up data. Patients received acupuncture either twice per week for 4 weeks (25 patients) or once per week for 6 weeks (12 patients). The primary end point was change in score on the Brief Fatigue Inventory between baseline and 2 weeks after the final treatment. A baseline Brief Fatigue Inventory score of four or greater was an eligibility requirement for the trial.

Results
Patients had completed cytotoxic chemotherapy an average of more than 2 years previously. Baseline fatigue scores were high, with approximately half of the sample scoring in the "severe" range. Mean improvement following acupuncture was 31.1% (95% CI, 20.6% to 41.5%), meeting our prespecified criterion for declaring acupuncture worthy of further study. Increasing age was associated with poorer response and failure to complete the study. There was no important difference in improvement following once-weekly and twice-weekly treatments.

Conclusion
Acupuncture is worthy of further study in the treatment of postchemotherapy fatigue.

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INTRODUCTION

Fatigue is a distressing symptom commonly experienced by cancer patients. An inherent symptom of advanced cancer,[1] fatigue is also an adverse effect of both chemotherapy[2] and radiotherapy,[3] often persisting after cessation of treatment.[4,5]

Anemia is one cause of fatigue in cancer patients. Treatment with erythropoietin improves anemia and reduces fatigue.[6] However, fatigue is not always associated with anemia, nor is it uniformly or completely dissipated by its treatment. Fatigue seems to be a complex, multifactorial problem, associated with physical, cognitive, emotional, and social correlates.[7] Although fatigue associated with cancer therapies has received mounting attention, there have been few studies of chronic posttreatment fatigue.

Acupuncture has been the focus of increasing research activity in recent years. Though best known for the treatment of pain, with randomized trials showing benefit in both acute and chronic pain,[8] acupuncture has been used to treat a wide variety of conditions, including fatigue.[9] There seems to be a lack of systematic research on acupuncture for fatigue, though anecdotal reports suggest benefit in chronic fatigue syndrome.[10,11]

In the present article, we report the results of a single-arm, phase II, pilot study of acupuncture for cancer fatigue. Our objective is to determine whether further research is warranted, rather than draw conclusions

about efficacy. The study design was adapted from phase II trials of chemotherapy and represents a novel approach to early-phase treatment studies with symptom control end points. The key aspect of a phase II trial is specification of an "uninteresting" and a "desirable" level of activity. Phase II designs require that, for an intervention to be taken forward to randomized trial, statistical analysis must reject a null hypothesis that it has uninteresting activity and fail to reject an alternative hypothesis that it has desirable activity. We defined "uninteresting" and "desirable" levels of activity as percentage mean changes from baseline. To reflect clinical realities, we considered that cancer patients in the future would not bear the time and trouble of a course of acupuncture if their fatigue improved by only 15%, but that a 40% improvement would be perceived as desirable. The decision rule adopted for considering acupuncture worthy of further study was that the 95% CI for the percentage change in fatigue must exclude improvements less than 15% and include improvements of at least 40%.

PATIENTS AND METHODS

We recruited ambulatory adult patients at Memorial Sloan-Kettering Cancer Center (MSKCC) who had completed cytotoxic chemotherapy at least 3 weeks previously but complained of persisting fatigue. Patients could be referred by physicians if they presented with fatigue or could self-refer in response to flyers posted in patient waiting areas. A research study assistant (B.F.) screened individuals for eligibility by direct interview and with reference to medical records.

Patients were excluded for severe anemia, which was defined as any of the following: hemoglobin level less than 9 g/dL, hematocrit level less than 30, decline in hemoglobin of $\geq$ 2 g/dL in the previous month, or active treatment for anemia. Other exclusion criteria were: Karnofsky Performance Status below 70, any significant comorbidity, anticipated survival of less than 3 months, acupuncture treatment in the previous 6 months, and fatigue before cancer diagnosis. None of the following could be scheduled during or for 3 weeks before the start of the trial: surgery, chemotherapy, radiotherapy, initiation of hormonal therapy, or initiation of immunotherapy.

Patients completed the Brief Fatigue Inventory (BFI) and the Hospital Anxiety and Depression Scale (HADS) at baseline. The BFI has been shown to have good reliability (Cronbach's $\alpha = .96$) and to correlate well with other measures of fatigue.[12] The instrument consists of a one-page fatigue assessment tool that contains nine items, each measuring the severity of fatigue on a 0-through-10 scale. The first three items assess current level of fatigue, and worst and usual fatigue in the preceding 24 hours. Six items assess the extent to which fatigue has interfered with different aspects of life, such as work or social relations, during the preceding 24 hours. The BFI score is calculated from the mean of completed items. HADS is a widely used instrument developed especially for populations with physical illness. It avoids aspects of psychological disease (eg, lowered sex drive) that may result directly from physical illness or its treatment. HADS has good psychometric properties[13,14]; a meta-analysis of studies using HADS reported a mean Cronbach's α of .83 for anxiety and .82 for depression.[15] HADS involves one measure ("I feel as if I am slowed down.") that is likely to be scored highly by a fatigued population. We therefore omitted scoring of this question. The scores for the remaining questions on the depression scale were multiplied by 7/6 to maintain comparability with the full HADS. This methodology has been used in a previous study of HADS in fatigued patients.[16] Baseline questionnaires were completed by interview with the research study assistant.

Patients with baseline BFI scores rounded to 4 or greater (considered the threshold between "mild" and "moderate" symptoms[12]) and HADS depression score less than 11 (the typical threshold for diagnosis of clinical depression) were given informed consent by an oncologist and enrolled onto the study.

A second baseline BFI was administered 1 week later at the clinic, immediately before the first acupuncture treatment. Follow-up BFIs were completed by patients at home 1 and 2 weeks after the final treatment. At a final debriefing interview, patients were asked to report any adverse effects from acupuncture and to describe any treatments taken for anemia or fatigue.

In the first stage of the study, patients received traditional Chinese acupuncture twice per week for 4 weeks. Treatment was given at the MSKCC Bendheim Integrative Medicine Service outpatient center—a tranquil facility a few blocks from the main MSKCC campus—by acupuncturists who were staff members of the MSKCC Integrative Medicine Service and licensed to practice acupuncture in New York State. Needles were inserted bilaterally at the following acupuncture point locations: ST36, SP8, and SP9. Unilateral needling was used at locations CV6, CV4. The point LI11 was needled bilaterally, except in cases in which axillary lymph node dissection presented the danger of lymphedema, in which case the affected arm was not needled. These points typically are used in Chinese medicine to treat fatigue.[17] Needles were inserted to the depth used in traditional Chinese acupuncture, and retained for 20 minutes. As is common in traditional acupuncture, practitioners attempted to elicit *de qi* to help determine exact point location. Immediately after needle insertion, acupuncturists completed an audit sheet verifying the acupuncture points used. These records were routinely reviewed, and acupuncturists were found to have followed the acupuncture point prescription.

Some patients in the initial cohort reported that twice-weekly treatment was inconvenient. Accordingly, we accrued additional patients in a second cohort who were treated once weekly for 6 weeks. We also slightly modified the acupuncture point prescription to the following: ST36, SP6, CV6, CV4, KI3, and KI27.

Statistical analyses were conducted using Stata 7 (Stata Corp, College Station, TX). Percent improvement was calculated for each patient by subtracting the mean of the two follow-up scores from the mean of the two baseline scores, and dividing by the latter. Acupuncture was to be considered worthy of further study if the 95% CI for percent improvement excluded 15% and included 40% or more. Predictors of improvement were explored by linear regression with percent improvement as the dependent variable. In the initial step, age, sex, days since chemotherapy, and baseline fatigue were assessed univariately. Anxiety and depression, which are highly correlated, were assessed in a bivariate model. Variables that predicted outcome ($P < .1$) were entered into a multivariable model.

Our initial sample size calculation was that 15 patients were required to have an 80% power to declare acupuncture active if the true improvement was 40%. Accrual to the first stage of the study was stopped when we received the data from the 15th patient.

Accrual to the second stage was stopped when all patients who had joined a waiting list had been contacted.

The study was approved by the institutional review board at MSKCC in accordance with an assurance filed with and approved by the US Department of Health and Human Services. Informed consent was obtained from each participant.

RESULTS

Initial recruitment interviews were conducted with 83 patients. Seventeen declined participation, predominantly due to travel constraints or concurrent illness, and 29 were excluded for the following reasons: recent acupuncture in five patients (17%); anemia in one patient (3%); recent change in treatment in three patients (10%); comorbidity in two patients (7%); high depression score in seven patients (24%); fatigue not related to chemotherapy in two patients (7%); low performance status in two patients (7%); low baseline fatigue score for six patients (21%); and recent chemotherapy in one patient (3%). Twenty-five patients were accrued for the first stage of the study between June 2001 and April 2002; of these, six withdrew. Three patients dropped out because of travel time considerations; two, before receiving any treatment; and one, after receiving three sessions of acupuncture. One patient experienced a recurrence of cancer during the trial and had to resume chemotherapy. Two patients withdrawing after three and five treatments reported that pain related to comorbidities made traveling to receive treatment overly troublesome. A second cohort of 12 patients was accrued between July 2002 and October 2002. All 12 provided follow-up data suggesting greater acceptability of once-weekly treatment.

Baseline characteristics of the sample are presented in Table 1, separately for the 31 patients who completed the trial and the six who did not provide follow-up data. Most patients had been treated with curative intent and had no evidence of disease. Despite patients having completed cytotoxic chemotherapy an average of more than 2 years previously, baseline fatigue scores were high, with approximately half of the sample scoring in the "severe" range ($\geq$ 7).[12] All patients completed the requisite number of treatments except for one in each cohort who missed a single treatment session. Similarly, one patient in each cohort exceeded the anticipated duration of treatment by 1 week.

The results of the study are presented in Table 2. The mean improvement from baseline to follow-up was 31.1% (standard deviation, 28.4). Twelve patients (39%) improved by 40% or more, and three experienced near-total ($>$ 75%) resolution of fatigue symptoms. Three patients experienced exacerbations in fatigue (increases of 5%, 18%, and 22%).

The 95% CI for improvement in fatigue is 20.6% to 41.5%, which meets the prespecified criterion for declaring acupuncture to be worthy of further study.

Table 1. Baseline Characteristics of the Study Sample

	Completed Study		Withdrawals	
	No. of Patients	%	No. of Patients	%
Total No.	31		6	
Male-female ratio	10:21	32:68	1:5	17:83
Diagnosis				
Breast cancer	10	32	1	17
Gastrointestinal cancer	3	10	0	0
Gynecologic cancer	5	16	0	0
Hematologic cancer	5	16	4	67
Lung cancer	7	23	0	0
Prostate cancer	0	0	1	17
Testicular cancer	1	3	0	0
KPS score				
70	1	3	0	0
80	8	26	2	33
90	18	58	3	50
100	4	13	1	17
Concurrent hormonal therapy	8	26	0	0
No evidence of disease	26	84	5	83
Age				
Mean	61		76	
SD	10.2		9.7	
Range	43-78		66-85	
Years since chemotherapy				
Mean	2.5		1.8	
SD	2.6		2	
Range	0.2-9.5		0.1-5.3	
Mean baseline BFI				
Mean	6.47		5.64	
SD	1.21		1.38	
Range	4.4-8.8		3.7-7.9	
HADS depression score				
Mean	4.5		5.2	
SD	2.1		2.9	
Range	0-9		1-9	
HADS anxiety score				
Mean	8.2		8.8	
SD	3.9		2.7	
Range	1-16		4-12	

Abbreviations: KPS, Karnofsky performance status; SD, standard deviation; BFI, Brief Fatigue Inventory; HADS, Hospital Anxiety and Depression Scale.

Age, depression, and anxiety predicted extent of improvement (Table 3). Improvement in fatigue was reduced by approximately 1% for each year increase in age and by 6.5% for a 1-point increase in HADS depression; in other words, younger and less depressed patients showed a greater response. Fatigue improved by an additional 3.5% for each 1-point increase in baseline anxiety. Sex was not predictive of improvement. Neither baseline severity nor days since chemotherapy predicted improvement ($P = .9$ and $P = .5$, respectively, when added to regression model).

Dichotomizing the data into age less than 65 years and $\geq$ 65 years, we find that older patients are more likely to drop out (6 of 18 *v* 0 of 19; $P = .006$ by χ^2) and have a

Table 2. Fatigue Scores During the Study

	No. of Patients	Mean	SD
First baseline BFI	31	6.60	1.39
Second baseline BFI	31	6.33	1.28
First post-treatment BFI	29*	4.54	2.18
Second post-treatment BFI	29†	4.36	2.17
Mean of baseline BFIs	31	6.47	1.21
Mean of posttreatment BFIs	31	4.55	2.16

Abbreviations: SD, standard deviation; BFI, Brief Fatigue Inventory.
*Two patients completed the second, but not first posttreatment BFI.
†Two patients completed the first, but not second posttreatment BFI.

tendency for poorer response (mean improvement, 19% *v* 38%, $P = .068$ by χ^2). It is of note that the mean improvement in the 19 patients younger than 65 years (38%; 95% CI, 25% to 52%) is close to our target.

We saw no evidence that frequency of treatment affects response. Improvements were slightly greater in patients receiving weekly treatment (33% *v* 30%; adjusted difference between groups, 2%; 95% CI, −19% to 24%). Adjustments for age, depression, anxiety, or baseline score did not affect this conclusion. We therefore recommend weekly treatment for further study.

No adverse events attributable to acupuncture were reported, and no patient used nonstudy treatments for fatigue or anemia.

DISCUSSION

The improvement in fatigue scores following acupuncture for chronic postchemotherapy fatigue met our prespecific criterion for declaring acupuncture to be worthy of further study. Although mean improvement for the whole sample (31%) is less than we had deemed desirable (40%), it is clinically meaningful. Moreover, we found that increasing age was significantly associated with poorer response; fatigue scores in patients younger than 65 years fell by 38%, which was very close to our target.

Given the single-arm, pilot design of our study, neither regression to the mean nor nonspecific (placebo) effects can be excluded as possible explanations for the observed improvements. We therefore intend to conduct a randomized placebo-controlled trial, restricting eligibility to patients younger than 65 years.

Table 3. Predictors of Percentage Improvement in Fatigue Scores by Multivariable Regression

Predictor	Coefficient	95% CI	*P*
Age	−0.95	−1.86 to −0.04	.04
Modified HADS depression score	−6.5	−11.7 to −1.3	.02
HADS anxiety score	3.5	0.6 to 6.3	.02

NOTE. All coefficients are in the original scale (unstandardized).
Abbreviation: HADS, Hospital Anxiety and Depression Scale.

An effect of acupuncture on fatigue is plausible given the mechanisms underlying each. Serotonin pathways are thought to have a role in mediating chronic fatigue.[18] Increased serotonin has been demonstrated in patients with chronic fatigue syndrome[19]and some cancers,[20] and a link between serotonin and cancer-related fatigue has been postulated.[21] Evidence that acupuncture reduces nausea[22-24] suggests that it may modify serotonin pathways; moreover, changes in serotonin following acupuncture have been directly measured in human acupuncture studies.[25] Given that we did not evaluate serotonin levels, a serotonergic mechanism for acupuncture effects remains speculative; a variety of psychologic and physiologic mechanisms may contribute to any effects of acupuncture against fatigue.

Patients seem to be interested in the use of acupuncture to treat fatigue. Most found the procedure to be very relaxing, and they enjoyed receiving treatment. Patients were eager to participate. The main obstacle to accrual was travel. MSKCC is situated in Manhattan, NY, but the center treats patients throughout the Tristate area as well as more distant regions. Traveling to the city to receive acupuncture was difficult for many patients, especially given the nature of the presenting condition.

We found that increasing age and depression scores were independently associated with poorer outcome. Regarding age, it may be that fatigue in older patients is intensified as a natural part of the ageing process. With respect to depression, it seems that even subclinical levels of depression may reduce the effect of treatment for fatigue. Increased baseline anxiety predicted a better outcome, possibly because acupuncture leads to reductions in tension and anxiety, resulting in decreases in arousal-related fatigue. However, given the design of this phase II study, we are unable to provide definitive explanations for these findings.

In conclusion, we believe that randomized trials of acupuncture for the treatment of postchemotherapy fatigue are warranted.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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