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Acupuncture for reduction of symptom burden in multiple myeloma patients undergoing autologous hematopoietic stem cell transplantation: a randomized sham-controlled trial

Gary Deng¹, Sergio Giralt², David J. Chung², Heather Landau², Jonathan Siman¹, Benjamin Search¹, Marci Coleton¹, Emily Vertosick³, Nathan Shapiro³, Christine Chien³, Xin S. Wang⁴, Barrie Cassileth¹, and Jun J. Mao¹

¹Integrative Medicine Service, Memorial Sloan Kettering Cancer Center, 1429 First Avenue, New York, NY 10021, USA

²Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

³Health Outcomes Research Group, Memorial Sloan Kettering Cancer Center, New York, NY, USA

⁴Department of Symptom Research, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract

Purpose—Hematopoietic stem cell transplantation (HCT) is potentially curative for a number of hematologic malignancies, but is associated with high symptom burden. We conducted a randomized sham-controlled trial (RCT) to evaluate efficacy and safety of acupuncture as an integrative treatment for managing common symptoms during HCT.

Methods—Adult patients with multiple myeloma undergoing high-dose melphalan followed by autologous HCT (AHCT) were randomized to receive either true or sham acupuncture once daily for 5 days starting the day after chemotherapy. Patients and clinical evaluators, but not acupuncturists, were blinded to group assignment. Symptom burden, the primary outcome was assessed with the MD Anderson Symptom Inventory (MDASI) at baseline, during transplantation, and at 15 and 30 days post transplantation.

Gary Deng, dengg@mskcc.org.

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Compliance with ethical standards This study was approved by the Institutional Review Board (IRB) at Memorial Sloan Kettering Cancer Center. All procedures performed were in accordance with the ethical standards of the institutional research committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest Dr. Giralt has received honoraria from Celgene, Takeda, Amgen, Jazz, and Sanofi; served in a consulting/advisory role for Celgene, Takeda, Sanofi, Jazz, Amgen, and Janssen; received research funding from Celgene and Takeda. Dr. Landau has received honoraria from Takeda; served in a consulting/advisory role for Onyx, Spectrum, Takeda, and Prothena; received research funding from Onyx. The remaining authors declare no competing financial interests.

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Trial registration NCT01811862

Results—Among 60 participants, true acupuncture produced nonsignificant reductions in overall MDASI core symptom scores and symptom interference scores during transplantation ($P = .4$ and $.3$, respectively), at 15 days ($P = .10$ and $.3$), and at 30 days posttransplantation ($P = .2$ and $.4$) relative to sham. However, true acupuncture was significantly more efficacious in reducing nausea, lack of appetite, and drowsiness at 15 days ($P = .042$, $.025$, and $.010$, respectively). Patients receiving sham acupuncture were more likely to increase pain medication use posttransplantation (odds ratio 5.31, $P = .017$).

Conclusions—Acupuncture was well tolerated with few attributable adverse events. True acupuncture may prevent escalation of symptoms including nausea, lack of appetite, and drowsiness experienced by patients undergoing AHCT, and reduce the use of pain medications. These findings need to be confirmed in a future definitive study.

Keywords

Acupuncture; Multiple myeloma; Hematopoietic stem cell transplantation; Symptom management; Complementary therapies; Integrative medicine

Introduction

Hematopoietic stem cell transplantation (HCT) is a potentially curative treatment and standard of care for a number of hematological malignancies [1]. Of over 15,000 allogeneic transplantations performed annually worldwide, nearly half are for acute leukemias, whereas in over 30,000 autologous transplantations, two-thirds are used to treat multiple myeloma or non-Hodgkin's lymphoma [2, 3]. HCT is often preceded by high-dose myeloablative conditioning chemotherapy, which causes significant acute side effects including pain from mucositis, poor appetite, fatigue, disturbed sleep, nausea, vomiting, and diarrhea. Symptoms are usually mild at baseline, intensify during conditioning chemotherapy, peak at the nadir of blood counts, and decrease by 30 days posttransplant [4–6]. These symptoms significantly hinder patient quality of life [7–9].

The current management of symptoms is mainly pharmacologic, with the use of analgesics, antiemetics, anxiolytics, and hypnotics. If used for prolonged periods, these medications in turn have detrimental side effects such as constipation, drowsiness, fatigue, and addiction. Investigation of other treatment options is therefore warranted.

Acupuncture is a complementary medicine modality that involves the insertion of needles into certain points on the body and their subsequent stimulation by manual manipulation, electrical pulse, or heat [10]. Neuroscience research suggests the effects of acupuncture are mediated via modulation of nervous system activities [11–14]. A Cochrane review of 11 randomized controlled trials (RCTs) concluded that acupuncture helps reduce chemotherapy-induced nausea and vomiting [15]. The “dose” of acupuncture varies among the studies. In one of the largest studies of breast cancer patients ($N = 104$), acupuncture was usually given at the PC-6 point once daily for 5 days after chemotherapy [16]. In a more recent study of 103 gynecological cancer patients for delayed nausea and vomiting, acupuncture was given at the PC-6 point once before chemotherapy and once the day after [17]. Systematic reviews of RCTs also support its analgesic effects [18, 19]. Further,

acupuncture may be beneficial in the management of hot flashes, xerostomia, or fatigue [20–23].

Given the high prevalence of multiple symptoms associated with conditioning chemotherapy in HCT patients and the limitations of current pharmacological symptom management strategies and indications, acupuncture may have the potential to be part of a multimodality transplantation care plan by targeting multiple symptoms. To our knowledge, no acupuncture trial has been conducted in the HCT population. Therefore, we conducted an RCT to generate preliminary data regarding the efficacy and safety of acupuncture in reducing symptoms in multiple myeloma patients undergoing autologous HCT. In addition, we compared results from our trial with historical data [8] to estimate the overall magnitude of benefit with acupuncture for patients undergoing HCT. Further, we explored the specific symptoms for which true acupuncture was the most efficacious relative to sham acupuncture control. The primary objective was to obtain preliminary evidence as to whether acupuncture reduces common symptoms experienced by patients undergoing conditioning chemotherapy and hematopoietic stem cell transplantation. Secondary objectives were to assess the effect size for each symptom, the subpopulation which would be more likely to respond to the intervention, the sample size for a future definitive efficacy study, and to explore correlations between reduction of symptoms and reduction of inflammation biomarkers, and whether acupuncture may reduce the use of symptom control medications or quality of sleep (reported separately).

Methods

Study design

We conducted a prospective, parallel randomized, sham-controlled, and subject- and evaluator-blinded acupuncture trial between May 2013 and January 2016 at Memorial Sloan Kettering (MSK) Cancer Center, an academic cancer center in an urban setting. The research protocol was approved by the Institutional Review Board at MSK and registered at clinicaltrials.gov before subject enrollment. The trial was registered at www.clinicaltrials.gov as #NCT01811862.

Study subjects

Multiple myeloma patients who were scheduled for autologous HCT at MSK were screened for eligibility and approached for written informed consent when eligible. Patients met the criteria for enrollment if they were age 21 or older with a diagnosis of multiple myeloma and scheduled to receive high-dose melphalan conditioning chemotherapy followed by autologous peripheral blood HCT. Exclusion criteria were absolute neutrophil count (ANC) less than 200/ μ l, platelet count less than 20,000/ μ l, and acupuncture treatment in the preceding 4 weeks prior to day 1.

Randomization

MSK's Clinical Research Database system (an institution-wide computer system used to achieve allocation concealment in all randomized trials in the cancer center) was used to randomize patients to receive either true or sham acupuncture, stratified by whether they

were receiving inpatient or outpatient chemotherapy using blocks of randomly permuted length. Only the treating acupuncturist was informed of the allocation of a patient to a group after randomization by the system.

Intervention

Study subjects received conditioning chemotherapy on day – 2 and stem cell infusion on day 0. Either true or sham acupuncture started on day – 1 and treatments were delivered on the same schedule in both arms. The interventions continued for a total of 5 days (when patients start to become neutropenic) or until ANC dropped below 200/ μ l or platelet count dropped below 20,000/ μ l whichever was sooner. Regardless of group assignment, every patient received the same usual pretransplantation and posttransplantation care that other patients undergoing conditioning chemotherapy in preparation for HCT received at MSK.

Licensed acupuncturists on MSK staff provided acupuncture treatments once daily in the patient's hospital room for inpatient transplantation, or at the clinic for outpatient transplantation. Each treatment was 20 min in duration. After reviewing the literature of previous studies and by consensus among the acupuncturists, the following acupuncture points were selected: GV20, Ex-HN3, HT7, PC6, ST36, SP6, KI3, LR3, and Ear Shen Men. Acupuncture needles (36 gauge $\times$ 40 mm length and 40 gauge $\times$ 30 mm length) manufactured by Seirin Corporation (Shizuoka, Japan) were used. No electric stimulation or heat was applied to the needles.

Sham acupuncture was delivered using a validated method as previously reported [24, 25], and the frequency and duration was identical to that of the true acupuncture group except without needle insertion into the skin. The acupuncturist tapped an empty plastic acupuncture needle guide tube on the bony area next to each acupuncture point to produce some discernible sensation, and then taped a needle with a piece of adhesive tape to the dermal surface for 20 min. In both groups, the patients' eyes were covered with patches so they could not view the treatment procedure.

Evaluation

The primary outcome was symptom burden as measured by the MD Anderson Symptom Inventory (MDASI) [26], a multi-symptom patient-reported outcome measure for clinical and research use. It has been validated in multiple myeloma and HCT patients [27]. The MDASI's 13 core symptom items include those that have been found to have the highest frequency and/or severity in patients with various cancers and treatment types. A component score for the MDASI symptom severity scale is obtained by taking the average of the 13 items together. The MDASI also contains 6 items measuring interference of daily activities by symptoms.

Baseline assessment was obtained within 1 to 2 weeks before conditioning chemotherapy. The MDASI was then assessed daily from day – 2 to day 5 (stem cell infusion was at day 0), at the first posttransplantation follow-up visit around day 15, and at the second follow-up visit around day 30.

The use of four classes of medications (both name and total daily dosage of each drug in the categories of analgesics, antiemetics, anxiolytics, and hypnotics) was recorded at baseline and on days 5, 15, and 30. Adverse events were monitored daily, when patients were hospitalized or visiting the clinic, and during the first and second follow-up visits.

Masking—Trial participants were blinded to treatment allocation. Study outcomes were collected by research assistants and laboratory personnel who were blinded to group assignment. Biostatisticians were also blinded to group assignment. Only the acupuncturists were aware of a patient's group assignment. Effectiveness of blinding was assessed by asking patients to guess to which group they were assigned.

Data analyses

Patients were considered evaluable if they provided both baseline and day 5 assessments. Patient data was analyzed according to randomization allocation regardless of the number of treatments received. All analyses were performed using Stata 13 (StataCorp, College Station, TX).

The primary comparison was the mean daily scores of MDASI total symptom scores and interference scores between the true and sham acupuncture groups. MDASI results during the peri-transplant period were calculated by plotting MDASI scores between days 0 and + 5 and calculating the area underneath this curve across all 6 days during transplant. This area was then divided by 6 to be comparable to the daily scores. MDASI scores were also assessed as the average scores on the day of first and second follow-up.

To assess whether there was a difference between treatment arms, we used analysis of covariance (ANCOVA) models adjusted for baseline MDASI score and type of chemotherapy (inpatient vs outpatient), as this was used to stratify randomization. To determine whether baseline characteristics predicted response to acupuncture, we added terms to the ANCOVA model to identify interactions between treatment arm and age, type of chemotherapy, and baseline MDASI score. To compare MDASI scores in the acupuncture groups with historical control in a post hoc analysis, we calculated the 95% confidence intervals (95% CIs) at each time point and obtained *P* values by *t* test.

To assess the change in medication use from baseline to day 5, we compared the total dosage of every drug in the four categories of medications (analgesics, antiemetics, anxiolytics, and hypnotics) and rated use of medications as (1) “decreased from baseline,” (2) “stayed the same from baseline,” or (3) “increased from baseline.” Both the number of medications and the dosages were taken into consideration. We then used ordinal regression for each of the four categories of medication with baseline use (some vs none) and inpatient chemotherapy as covariates to calculate the odds ratio (OR) of each scenario.

Power considerations

The study was powered to estimate the effect size of acupuncture. For a study with 30 patients in each of two groups, a continuous outcome measure, the standard error for the difference between groups will be close to 0.25 standard deviations of the outcome. We predicted that the observed standard error would be around 0.23 due to the inclusion of a

predictive baseline covariate in the analysis. We decided to declare acupuncture worthy of further study if a one-sided 90% CI included a standardized difference of at least 0.5.

Results

The flow of study participants through the trial is shown in the CONSORT chart (Fig. 1). Of 63 patients who were randomized, 2 withdrew consent prior to receiving the true acupuncture intervention and 1 withdrew after receiving the sham acupuncture intervention without providing the primary endpoint. Of 60 evaluable patients, 29 were from the true acupuncture group and 31 from the sham acupuncture group. Patient characteristics in the 2 groups were well matched (Table 1).

Symptom changes during HCT between groups

Comparison of MDASI overall scores between groups is shown in Table 2. Overall symptom scores were lower in the true acupuncture group, but between-group differences did not reach statistical significance for either MDASI symptom or symptom interference scores (Table 2). The 95% CI of the reduction included a standardized difference of at least 0.5 (Table 2, Column “95% CI”), meeting an a priori criterion that deemed acupuncture worthy of further study. Individual symptoms that were reduced more significantly in the true acupuncture group were nausea, lack of appetite, and drowsiness at first follow-up (all $P < .05$, Table 3). There were no significant differences between groups in other symptoms.

A subgroup analysis by type of chemotherapy found evidence that reduction of symptoms were more prominent among patients receiving inpatient chemotherapy (Table 4).

Time course of changes in MDASI symptom scores for patients treated with true or sham acupuncture are shown in Fig. 2. In both groups, the symptoms curves (the component score of core symptoms) stayed relatively flat and closer to baseline, rather than the crescendo-decrescendo course that is normally expected, but with the true acupuncture group having less severe symptoms. Peak of symptom burden at nadir is a well documented phenomenon in HCT patients. With this surprising finding, we conducted a post hoc analysis comparing data in this trial to historical controls in order to estimate how much the reduction of symptoms could be. A time course curve derived from a previous non-intervention prospective study is included in Fig. 2 to show the blood-count-nadir-related high symptom burden during HCT. At day 5, when symptoms are expected to be the worst, the MDASI core symptoms score was 3.50 (SD 1.42, 95% CI 3.03 to 3.97) in the historical data, whereas it was 1.38 (SD 1.66, 95% CI 0.75 to 2.01) in the true acupuncture group of this study ($P < .0001$). The differences between true acupuncture and historical control were highly significant ($P < .001$ for all time points from day 0 onward), whereas the difference between sham acupuncture and historical control was only highly significant for day 5 ($P < .001$) and moderately significant for day 0 ($P = .04$).

Safety of acupuncture

Acupuncture was well tolerated. There were no significant differences in incidence of adverse events related to acupuncture between the two groups (Online Resource 1a, b). Two patients in the sham acupuncture group were admitted to the intensive care unit (ICU) for

events judged unrelated to the sham procedure. No patients in the true acupuncture group were admitted to the ICU.

Medication use by groups

We investigated the effect of acupuncture on the use of analgesic, antiemetic, anxiolytic, and hypnotic medications at day 5 using ordinal logistic regression. We found that patients receiving true acupuncture were more likely to have decreased analgesic use or to have kept analgesic use the same compared with sham patients (Online Resource 2). To investigate this association further, we created a logistic regression model for the outcome of increasing analgesic medication use from baseline to day 5, adjusting for baseline analgesic use and type of chemotherapy. Patients in the sham acupuncture group had greater than five times the odds of increasing analgesic medications from baseline compared with those in the true acupuncture group (OR 5.31, 95% CI 1.35 to 20.93, $P = .017$).

Masking

Subject guesses as to treatment allocation at the post-study debriefing are shown in Online Resource 3. Credibility scores were very similar in each group ($P > .9$), suggesting that blinding was maintained. Regardless of the group to which patients were randomized, participants guessed that they were in the true or sham acupuncture group in roughly equal frequencies.

Discussion

HCT is associated with heavy symptom burden, compromising patient quality of life, and can lead to posttransplantation complications. With current standard peri-transplantation care, symptom burden rises shortly after conditioning chemotherapy, peaks at nadir, and gradually recovers over the next 30 days [4–6, 9]. Pharmacologic interventions are the mainstay of current symptom management plans. Other therapeutic interventions need to be investigated.

In this RCT, we examined the role of acupuncture as an integrative treatment to help manage symptoms in HCT patients. The study was powered to estimate the effect size of acupuncture, not to definitively prove the efficacy of acupuncture by rejecting a null hypothesis. We found there was an overall nonsignificant trend indicating that true acupuncture reduced symptoms more than sham acupuncture. However, there were significant improvements in nausea, appetite change, and drowsiness, as well as reduced pain medication use. Acupuncture was safe with few attributable adverse events. Our findings suggest that acupuncture has the potential to help manage certain symptoms in patients undergoing HCT.

Although the finding of lower overall symptom scores with true acupuncture did not reach statistical significance, it did meet a predefined criterion that deemed acupuncture worthy of further investigation (Table 2). There are three possible reasons for this finding: (1) the sample size of the study was too small (the study was powered to estimate the effect size), (2) there was no difference between true and sham acupuncture in reducing overall symptom burden, or (3) signals were diluted from symptoms not responsive to the specific needling of

acupuncture. MDASI is a composite of 13 core symptoms. For acupuncture to reduce the MDASI overall score significantly, it needs to either consistently reduce many symptoms to a modest degree or reduce a few symptoms to a large degree.

To explore which symptoms were reduced the most from acupuncture treatment, we investigated specific symptoms and found that true acupuncture reduced nausea, lack of appetite, and drowsiness more than sham acupuncture at 2 weeks post-HCT. Although pain scores were similar between the two groups, patients receiving true acupuncture used significantly less pain medication. At nadir, patients receiving sham acupuncture were five times more likely to increase the use of pain medications from baseline. This is the first time that acupuncture has been reported to have significantly reduced nausea and pain in HCT patients. Improvement in lack of appetite, one of the major symptom burdens in HCT, is not a well-known effect of acupuncture and may be related to reduction of nausea in this setting. Reduction of nausea and poor appetite can improve patient's nutritional status, aiding in their recovery from HCT. Reduction of drowsiness, another major symptom burden in these patients, is an interesting new finding that deserves further investigation. Clinically, it is also plausible that a reduction in the use of pain medications, which are often opioids, helps relieve patients' symptoms of nausea, lack of appetite, and drowsiness.

The time course of post-HCT symptoms is well established [9]. It follows a crescendo-decrescendo course, peaking at nadir [4–6, 28]. One of the challenges in post-HCT care is to “flatten the symptom curve.” A recently published RCT shows that palliative care can reduce symptom burden at 2 weeks (14 days) after admission for HCT, although the symptom burden was still above baseline (see Fig. 2 D of that publication) [28]. In our study, we observed such a flattening of the curve. Patients reported symptom burdens similar to baseline throughout the post-HCT course. Differences between the true acupuncture group and historical control in post-HCT symptoms were highly significant. As comparison between a trial and historical data is problematic because usual care patterns may not be exactly the same, our observation needs to be verified in an RCT where one group of patients receives only the usual standard post-HCT care.

Our study has several limitations. First, we had a small sample size to explore for efficacy. To verify these preliminary findings, a larger trial with more power needs to be conducted. Second, it did not include a usual-care control group. The lack of peak symptom burden at nadir that was seen in this study could be from either acupuncture or better post-HCT supportive care in the particular clinical setting in which this study was conducted. Third, we examined several secondary outcomes and raised the possibility of false discovery. These secondary findings need to be interpreted cautiously and require further verification. Lastly, we did not include allogeneic HCT patients, limiting the study's generalizability.

Despite these limitations, to our knowledge, this is the first trial examining acupuncture as an integrative approach for reducing multiple symptoms in the HCT setting. The strengths of our study include a randomized sham-controlled design, adequate blinding of patients to assignment of true or sham acupuncture, a good retention rate with few patients lost to follow-up, and evaluation of both short- and long-term effects (up to 30 days post-HCT).

Conclusion

In summary, we found that true acupuncture treatment, when integrated into the care of patients receiving autologous HCT, appears to be safe and leads to less severe symptoms of nausea, lack of appetite, and drowsiness than sham acupuncture. In addition, true acupuncture was associated with less use of pain medications. Patients receiving acupuncture did not experience peak symptom burden at post-HCT nadir. Future research with an adequate sample size that targets the specific symptoms and pain medication use identified by our study may help establish evidence for acupuncture as a part of HCT comprehensive care. If acupuncture can be shown to be effective in improving peri- or post-HCT care, patients will benefit from expanded treatment options during the difficult period of transplantation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Copelan EA (2006) Hematopoietic stem-cell transplantation. *N Engl J Med* 354(17):1813–1826. 10.1056/NEJMra052638 [PubMed: 16641398]
2. Gertz MA, Dingli D (2014) How we manage autologous stem cell transplantation for patients with multiple myeloma. *Blood* 124(6): 882–890. 10.1182/blood-2014-03-544759 [PubMed: 24973360]
3. Giralt S (2011) Stem cell transplantation for multiple myeloma: current and future status. *Hematol Am Soc Hematol Educ Program* 2011:191–196. 10.1182/asheducation-2011.1.191
4. Anderson KO, Giralt SA, Mendoza TR, Brown JO, Neumann JL, Mobley GM, Wang XS, Cleeland CS (2007) Symptom burden in patients undergoing autologous stem-cell transplantation. *Bone Marrow Transplant* 39(12):759–766. 10.1038/sj.bmt.1705664 [PubMed: 17438588]
5. Campagnaro E, Saliba R, Giralt S, Roden L, Mendoza F, Aleman A, Cleeland C, Weber D, Brown J, Anderson KO (2008) Symptom burden after autologous stem cell transplantation for multiple myeloma. *Cancer* 112(7): 1617–1624. 10.1002/cncr.23299 [PubMed: 18260091]
6. Mosher CE, Redd WH, Rini CM, Burkhalter JE, DuHamel KN (2009) Physical, psychological, and social sequelae following hematopoietic stem cell transplantation: a review of the literature. *Psycho Oncology* 18(2):113–127. 10.1002/pon.1399 [PubMed: 18677717]
7. Ramsenthaler C, Osborne TR, Gao W, Siegert RJ, Edmonds PM, Schey SA, Higginson IJ (2016) The impact of disease-related symptoms and palliative care concerns on health-related quality of life

- in multiple myeloma: a multi-centre study. *BMC Cancer* 16: 427 10.1186/s12885-016-2410-2 [PubMed: 27387201]
8. Wang XS, Shi Q, Shah ND, Heijnen CJ, Cohen EN, Reuben JM, Orlowski RZ, Qazilbash MH, Johnson VE, Williams LA, Mendoza TR, Cleeland CS (2014) Inflammatory markers and development of symptom burden in patients with multiple myeloma during autologous stem cell transplantation. *Clin Cancer Res* 20(5):1366–1374. 10.1158/1078-0432.CCR-13-2442 [PubMed: 24423611]
 9. Cohen MZ, Rozmus CL, Mendoza TR, Padhye NS, Neumann J, Gning I, Aleman A, Giralt S, Cleeland CS (2012) Symptoms and quality of life in diverse patients undergoing hematopoietic stem cell transplantation. *J Pain Symptom Manag* 44(2):168–180. 10.1016/j.jpainsymman.2011.08.011
 10. Kaptchuk TJ (2002) Acupuncture: theory, efficacy, and practice. *Ann Intern Med* 136(5):374–383 [PubMed: 11874310]
 11. Huang W, Pach D, Napadow V, Park K, Long X, Neumann J, Maeda Y, Nierhaus T, Liang F, Witt CM (2012) Characterizing acupuncture stimuli using brain imaging with fMRI: a systematic review and meta-analysis of the literature. *PLoS One* 7(4):e32960 10.1371/journal.pone.0032960 [PubMed: 22496739]
 12. Stone JA, Johnstone PA (2010) Mechanisms of action for acupuncture in the oncology setting. *Curr Treat Options in Oncol* 11(3–4): 118–127. 10.1007/s11864-010-0128-y
 13. Han JS (2011) Acupuncture analgesia: areas of consensus and controversy. *Pain* 152(3 Suppl):S41–S48. 10.1016/j.pain.2010.10.012 [PubMed: 21078546]
 14. Pyne D, Shenker NG (2008) Demystifying acupuncture. *Rheumatology (Oxford)* 47(8):1132–1136. 10.1093/rheumatology/ken161 [PubMed: 18460551]
 15. Ezzo JM, Richardson MA, Vickers A, Allen C, Dibble SL, Issell BF, Lao L, Pearl M, Ramirez G, Roscoe J, Shen J, Shivan JC, Streiberger K, Treish I, Zhang G (2006) Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. *Cochrane Database Syst Rev* 2:CD002285 10.1002/14651858.CD002285.pub2
 16. Shen J, Wenger N, Glaspy J, Hays RD, Albert PS, Choi C, Shekelle PG (2000) Electroacupuncture for control of myeloablative chemotherapy-induced emesis: a randomized controlled trial. *JAMA* 284(21):2755–2761 [PubMed: 11105182]
 17. Rithirangsiroj K, Manchana T, Akkayagorn L (2015) Efficacy of acupuncture in prevention of delayed chemotherapy induced nausea and vomiting in gynecologic cancer patients. *Gynecol Oncol* 136(1):82–86. 10.1016/j.ygyno.2014.10.025 [PubMed: 25449310]
 18. Greenlee H, Balneaves LG, Carlson LE, Cohen M, Deng G, Hershman D, Mumber M, Perlmutter J, Seely D, Sen A, Zick SM, Tripathy D, Society for Integrative O (2014) Clinical practice guidelines on the use of integrative therapies as supportive care in patients treated for breast cancer. *J Natl Cancer Inst Monogr* 2014(50):346–358. 10.1093/jncimonographs/igu041 [PubMed: 25749602]
 19. Vickers AJ, Cronin AM, Maschino AC, Lewith G, MacPherson H, Foster NE, Sherman KJ, Witt CM, Linde K, Acupuncture Trialists C (2012) Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med* 172(19):1444–1453. 10.1001/archinternmed.2012.3654 [PubMed: 22965186]
 20. Lau CH, Wu X, Chung VC, Liu X, Hui EP, Cramer H, Lauche R, Wong SY, Lau AY, Sit RS, Ziea ET, Ng BF, Wu JC (2016) Acupuncture and related therapies for symptom management in palliative cancer care: systematic review and meta-analysis. *Medicine (Baltimore)* 95(9):e2901 10.1097/MD.0000000000002901 [PubMed: 26945382]
 21. Garcia MK, Graham-Getty L, Haddad R, Li Y, McQuade J, Lee RT, Spano M, Cohen L (2015) Systematic review of acupuncture to control hot flashes in cancer patients. *Cancer* 121(22):3948–3958. 10.1002/cncr.29630 [PubMed: 26281028]
 22. Hackett KL, Deane KH, Strassheim V, Deary V, Rapley T, Newton JL, Ng WF (2015) A systematic review of non-pharmacological interventions for primary Sjogren's syndrome. *Rheumatology (Oxford)* 54(11):2025–2032. 10.1093/rheumatology/kev227 [PubMed: 26135587]
 23. Mao JJ, Farrar JT, Bruner D, Zee J, Bowman M, Seluzicki C, DeMichele A, Xie SX (2014) Electroacupuncture for fatigue, sleep, and psychological distress in breast cancer patients with

- aromatase inhibitor-related arthralgia: a randomized trial. *Cancer* 120(23): 3744–3751. 10.1002/cncr.28917 [PubMed: 25077452]
24. Lao L, Bergman S, Hamilton GR, Langenberg P, Berman B (1999) Evaluation of acupuncture for pain control after oral surgery: a placebo-controlled trial. *Arch Otolaryngol Head Neck Surg* 125(5):567–572 [PubMed: 10326816]
25. Lao L, Bergman S, Langenberg P, Wong RH, Berman B (1995) Efficacy of Chinese acupuncture on postoperative oral surgery pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 79(4):423–428 [PubMed: 7614199]
26. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, Engstrom MC (2000) Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer* 89(7):1634–1646 [PubMed: 11013380]
27. Jones D, Vichaya EG, Wang XS, Williams LA, Shah ND, Thomas SK, Johnson VE, Champlin RE, Cleeland CS, Mendoza TR (2013) Validation of the M. D. Anderson Symptom Inventory multiple myeloma module. *J Hematol Oncol* 6:13 10.1186/1756-8722-6-13 [PubMed: 23384030]
28. El-Jawahri A, LeBlanc T, VanDusen H, Traeger L, Greer JA, Pirl WF, Jackson VA, Telles J, Rhodes A, Spitzer TR, McAfee S, Chen YA, Lee SS, Temel JS (2016) Effect of inpatient palliative care on quality of life 2 weeks after hematopoietic stem cell transplantation: a randomized clinical trial. *JAMA* 316(20):2094–2103. 10.1001/jama.2016.16786 [PubMed: 27893130]

Fig. 1.
CONSORT diagram of study design and enrollment

Fig. 2. MDASI symptom scores from baseline to day 30 for patients in the acupuncture arm (green line), the sham arm (red line), and among a group of historical control patients receiving no acupuncture treatment (blue line).

Table 1Patient characteristics by treatment arm ($n = 60$)

	Acupuncture ($n = 29$)	Sham acupuncture ($n = 31$)
Age, y	59 (54, 66)	58 (55, 64)
Male	10 (34%)	12 (39%)
Inpatient chemotherapy	16 (55%)	18 (58%)
Mean MDASI core symptoms score	1.82 (SD 1.91, 95% CI 1.10 to 2.55)	1.98 (SD 1.35, 95% CI 1.48 to 2.47)

Data are reported as median (IQR) or frequency (%) for age, gender, and inpatient vs outpatient chemotherapy

Table 2

Component scores of core MDASI symptoms and symptom interference between groups

	True acupuncture (<i>n</i> = 29)	Sham acupuncture (<i>n</i> = 31)	Difference	95% CI	<i>P</i> value
MDASI Symptom score					
Days 0 to + 5	1.23 (1.24)	1.66 (1.14)	− 0.19	− 0.60 to 0.23	.4
First follow-up (around day 15)	1.34 (1.49)	2.10 (1.52)	− 0.47	− 1.03 to 0.09	.10
Second follow-up (around day 30)	1.15 (1.10)	1.67 (1.40)	− 0.37	− 0.92 to 0.18	.2
MDASI Symptom interference score					
Days 0 to + 5	1.76 (1.97)	2.53 (2.26)	− 0.42	− 1.17 to 0.33	.3
First follow-up (around day 15)	2.51 (2.63)	3.40 (2.54)	− 0.45	− 1.36 to 0.46	.3
Second follow-up (around day 30)	2.02 (2.15)	2.61 (2.35)	− 0.36	− 1.26 to 0.53	.4

Models were adjusted for baseline score and type of chemotherapy. Data are presented as mean (SD) and adjusted mean difference with 95% CI

Table 3

Specific symptom scores by treatment group and adjusted difference between groups [mean (SD)]

	Sham acupuncture (n = 31)	True acupuncture (n = 29)	Difference	95% CI	P value
Nausea					
Days 0 to + 5	1.96 (1.89)	1.13 (1.23)	0.44	− 0.21 to 1.10	.2
First follow-up	2.65 (2.82)	1.34 (2.64)	1.32	0.05 to 2.59	.042
Second follow-up	1.73 (2.27)	0.86 (2.17)	0.91	− 0.31 to 2.14	.14
Lack of appetite					
Days 0 to + 5	2.47 (2.00)	1.38 (1.51)	1.02	0.18 to 1.86	.019
First follow-up	3.03 (3.37)	1.45 (2.05)	1.45	0.19 to 2.71	.025
Second follow-up	2.10 (3.02)	1.66 (2.33)	0.34	− 1.01 to 1.69	.6
Drowsiness					
Days 0 to + 5	2.31 (1.78)	2.09 (1.77)	0.07	− 0.65 to 0.80	.8
First follow-up	2.55 (2.20)	1.21 (1.63)	1.22	0.31 to 2.12	.010
Second follow-up	2.17 (2.39)	1.41 (1.59)	0.62	− 0.19 to 1.44	.13

Table 4

Interaction models assessing whether the effect of acupuncture on MDASI score differed based on baseline characteristics. Interaction terms were included for the interaction between MDASI score and inpatient chemotherapy, age, or baseline MDASI score. The β for an interaction term is not interpretable, but is included to show the direction of interactions

	MDASI Symptom score			MDASI Interference score		
	B	95% CI	P value	β	95% CI	P value
Inpatient chemotherapy						
Days 0 to 5	- 0.24	- 1.07 to 0.60	.6	- 0.08	- 1.60 to 1.44	.9
First follow-up	- 0.38	- 1.50 to 0.74	.5	0.18	- 1.66 to 2.03	.8
Second follow-up	- 1.10	- 2.17 to - 0.03	.044	- 1.68	- 3.44 to 0.07	.060
Age	B	95% CI	P value	β	95% CI	P value
Days 0 to 5	0.03	- 0.02 to 0.08	.2	0.03	- 0.07 to 0.12	.6
First follow-up	- 0.02	- 0.09 to 0.05	.5	0.03	- 0.08 to 0.14	.6
Second follow-up	- 0.02	- 0.09 to 0.05	.5	- 0.02	- 0.13 to 0.09	.7
Baseline MDASI score	B	95% CI	P value	β	95% CI	P value
Days 0 to 5	- 0.12	- 0.43 to 0.19	.4	- 0.10	- 0.46 to 0.25	.6
First follow-up	- 0.16	- 0.57 to 0.26	.5	0.04	- 0.40 to 0.47	.9
Second follow-up	- 0.55	- 0.97 to - 0.14	.010	- 0.06	- 0.51 to 0.39	.8