

# Guidance for prospective acupuncture treatment on cancer-related fatigue (CRF)

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Fatigue is the most common symptom experienced by patients with cancer which is also one of the most common adverse effects that occur during and after cancer treatment. It has been defined as, “a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatments that is not proportional to recent activity and interferes with usual functions.” (1). Cancer patients express their fatigue as very serious, chronic, distressing and is not alleviated by the rest. Cancer treatment related fatigue generally improves post the completion of therapy, but some degree of fatigue may persist for months or years (2). Fatigue is reported in 14-96% of patients undergoing cancer treatment and in 19-82% of patients during post-treatment (3). Fatigue affects multiple aspects of cancer patients’ lives – physical, mental, and emotional – and has a significant negative impact on patients’ physical functioning and overall quality of life (QOL) (4). Fatigue has also been associated with shorter recurrence-free and overall survival in patients with cancer (5).

Breast cancer, that is the subject of the study by Molassiotis *et al.* (6), is the most common type of cancer among women and is the leading cause of death by cancer. It accounts for 23% (1.38 million) of new cancer cases and 14% of deaths caused by cancer worldwide (7). Fatigue is also a major complain in Breast cancer patients and survivors. They experiences a varying degree of fatigue during and after chemotherapy or radiotherapy (8).

Fatigue is a complex multidimensional symptom because it encompasses physical, mental, and emotional aspects (9). Therefore there are limited treatment options to alleviate this symptom and a variety of studies on effective treatments for cancer-related fatigue (CRF) have been

performed. According to several review articles on effective treatments for CRF, recommended interventions for CRF include non-pharmacological interventions, such as psycho-social interventions, exercise, sleep therapy, and acupuncture. Pharmacological interventions include stimulants, namely modafinil and methylphenidate. In some patients antidepressants may be beneficial. The non-pharmacological therapies of psycho-social interventions and exercise have the strongest evidence supporting use. Other non-pharmacological and pharmacological interventions have lesser supporting evidence but still may be effective for some patients (9,10).

Acupuncture is one of non-pharmacological therapies for CRF. It is a popular complementary therapy among cancer patients and some evidence suggests that it could potentially alleviate fatigue. Several studies examining the feasibility of acupuncture to manage CRF have been reported. A phase II uncontrolled study using acupuncture to treat post-chemotherapy fatigue by Vickers *et al.* (11) has shown that acupuncture improved fatigue by 31.1%. Patients received acupuncture either twice per week for 4 weeks (n=25) or once per week for 6 weeks (n=12). There was no important difference in improvement following once-weekly and twice-weekly treatments. The authors determined that acupuncture is worthy of further study in the treatment of post-chemotherapy fatigue. Molassiotis *et al.* (12) studied 47 cancer patients after chemotherapy in a randomized controlled trial with a 3-group design – acupuncture (n=15), acupressure (n=16) and sham acupressure (n=16). The acupuncture group received six 20-min sessions needling three points (LI4, SP6 and ST36) over 2 weeks, while the patients in the two acupressure groups were taught to

massage/press the points and did so daily thereafter for 2 weeks on their own. Improvements in fatigue were 36%, 19%, and 0.6% respectively. This study concluded that acupuncture shows great potential in the management of CRF, but it should be tested further using a large sample and a multicenter design. Balk *et al.* (13) compared effect of acupuncture on fatigue in cancer patients receiving external radiation therapy with sham acupuncture. Twenty-seven participants received acupuncture once to twice per week during the 6-week course of radiation therapy. Both true and sham acupuncture groups had improved fatigue, fatigue distress, quality of life, and depression from baseline to 10 weeks, but the differences between the groups were not statistically significant. This study also highlighted poor feasibility related to the use of the Park sham device. A study by Johnston *et al.* (14) examined the feasibility of delivering a patient education integrated with acupuncture for relief of CRF compared with usual care. Compared to usual care control, treatment group patients had improved fatigue. A promising effect was found, although recruitment was problematic with only 13 randomized participants. The most recent a pilot randomized controlled trial by Smith *et al.* (15) compared acupuncture with sham acupuncture and wait list controls. A total of 30 women with fatigue following breast cancer treatment participated in this trial. Women received six sessions of acupuncture over 8 weeks. There was a significant reduction in fatigue for women receiving acupuncture compared with control after 2 weeks, and a significant improvement in well-being at 6 weeks for acupuncture compared with the sham and wait list control. A critical review of complementary therapies for CRF (4) showed that acupuncture is promising in the management of fatigue but preliminary studies had small sample sizes and methodological limitations. Conclusions of these studies is the same that acupuncture have promising effectiveness for CRF but an appropriately powered trial to evaluate the effect of acupuncture is needed.

The study by Molassiotis *et al.* (6) is a large, multi-center, pragmatic randomized controlled trial (RCT) that is enrolled 302 women. This study was consistent with earlier other studies indicating a potential benefit from acupuncture. This study is methodologically more rigorous trial than earlier several uncontrolled small sample sizes preliminary trials (11,12). Therefore the study by Molassiotis *et al.* (6) provides more powerful evidence that acupuncture has beneficial effect on CRF.

But this study has some limitations and results should

be interpreted with caution. A pragmatic RCT applied to this study is research method that reflects a little more clinical practice than conventional RCTs. So the design of pragmatic RCTs reflect the heterogeneity of patients in general practice, minimize exclusion criteria, focus on groups with a wide range of diagnoses, define patient groups by presentation rather than diagnosis, which may not employ placebos and may not be blinded (16). This study also didn't include placebo group and was lack of blinding. So from results of this study, we may confirm effectiveness of acupuncture on CRF but can not identify efficacy of acupuncture on CRF. Although sham acupuncture is still an unresolved methodological issue in acupuncture clinical trials, future studies will be needed to compare real acupuncture with appropriate sham acupuncture to rule out a placebo effect of acupuncture and compare acupuncture with active control such as exercise or psycho-social interventions that have the strongest supporting evidence to better evaluate treatment-specific effects.

This study also didn't use strict inclusion or exclusion criteria, because of using pragmatic RCTs method, therefore it has few selective biases. Other various related factors of fatigue were not considered, such as comorbid chronic nonmalignant diseases (heart and lung diseases, diabetes, and depression) (17), duration of fatigue (range 2 to 69 months), and age (range 25 to 80 years). Thus further analysis of duration of fatigue, age, and the severity of fatigue is necessary. And of patients' ethnic background in composition difference between the groups, the misconception that asian, especially Chinese, are more favorable to acupuncture considering its familiarity would act as a bit of bias. Future studies will need to better characterize the patients and eligibility criteria based on the currently known and emerging contributors to fatigue.

Acupuncture points ST36, SP6, LI4 selected in this study is suitable for CRF in breast cancer patients, considering meridian distribution of breast and improving fatigue. However, acupuncture points was substandardized allowing therapists to have some flexibility, alternative points GB4 and SP9 on the legs instead of LI4 was selected in case of lymphedema. In clinical practice, needling should be avoided in lymphedematous limbs or limbs prone to lymphedema, in the ipsilateral arm in patients who have undergone axillary dissection-risk of lymphedema (18). Therefore further studies is needed to apply the most appropriate standardized points based on classic meridian theory and clinical practice. It will be better that main

selection points is points of *Yang Ming* meridian on the leg, and add some points of *Chongren* meridian on the abdomen related to female physiological function and stimulating vital energy (*Qi*) such as CV12, CV4, and some points on head or face with sedative effects.

It is known that acupuncture have short-term effects on CRF (11-13). In this study, the immediate effects after 6 weeks of acupuncture were only described and 10 and 18 weeks follow up results and long-term application possibility of acupuncture on CRF were not described. Cancer patients experience persistent fatigue after treatment. If acupuncture has only short-term effect on CRF, acupuncture for CRF will practically have limited applicability. Therefore additional studies on long-term effect of acupuncture for CRF is needed.

In conclusion, the best contribution of the study by Molassiotis *et al.* (6). is that it provides more powerful evidence on effectiveness of acupuncture for CRF. Currently, evidences on acupuncture for CRF is still insufficient and arguments on the effect of acupuncture for CRF will be continued. However, it has been known that traditionally primary mechanism of acupuncture is 'regulating *Qi* and treating *Shin*'. Many of researches on biological mechanism of acupuncture have supported possible analgesic and sedative effects of acupuncture (19,20). Hence it is still expected that acupuncture is positive effectiveness on CRF. Ultimately, further studies in large, randomized clinical trials are needed to assess the potential benefits of acupuncture for CRF. And it is needed to seek specific and practical acupuncture treatment protocol considering kinds of cancer, cancer stage, cancer treatment, and cancer treatment cycle and develop the most effective and safe clinical trial protocol of acupuncture for CRF based on many of evidences and clinical practice.

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