

Limiting Chemotherapy Side Effects by Using Moxa

Using daily self-administered indirect moxibustion to St 36 *zu san li* to reduce chemotherapy-induced pancytopenia: Study protocol for a feasibility study

Beverley de Valois, Teresa Young, Rob Glynne-Jones, Clare Scarlett and Friedrich Staebler

ABSTRACT

Background: This trial aims to investigate the feasibility of teaching cancer patients undergoing chemotherapy within the National Health Service (NHS) to self-administer daily indirect moxibustion to St 36 *zu san li*. This will begin to assess whether this intervention can reduce chemotherapy induced pancytopenia, specifically neutropenia, anaemia, and thrombocytopenia, and facilitate patients completing chemotherapy without delays or dose reduction.

Methods/Design: This uncontrolled, single-arm feasibility study aims to recruit 25 breast, colorectal or gynaecological cancer patients undergoing chemotherapy regimens for which granulocyte-colony stimulating factor (G-CSF) is not indicated. The primary outcome is adherence to daily self-administered moxibustion (the use of heat to stimulate a specific acupuncture point) measured by daily moxa diaries. This routine takes less than ten minutes per day, to be carried out for the duration of chemotherapy treatment (starting seven to ten days before the first cycle and continuing three weeks after the final cycle). Secondary measures include blood counts, variation to planned chemotherapy schedule, health related quality of life measured by FACT-An and FACT-N, Patient Activation Measure (PAM), chemotherapy related toxicities, and adverse events of moxibustion. Study participants will be taught the procedure in two meetings with the health improvement practitioner, who will assess their suitability and supply a kit containing the materials needed. Participants will be supported at home by a YouTube video and instruction leaflet detailing the procedure.

Discussion: Ethical approval was obtained in October 2015. There has been one subsequent protocol amendment, approved in March 2016. Recruitment opened on 29 February 2016. Data collection will be completed by November 2016.

Trial registration: UKCRN ID: **19916 (IRAS 186057)**

Keywords: Cancer, moxibustion, chemotherapy, neutropenia, leukopenia, anaemia, thrombocytopenia, self-care

BACKGROUND

Nearly 50% of cancer patients prescribed chemotherapy receive less than 85% of the planned dose, which has potential impacts on survival (Lyman, Dale et al. 2003; Crawford, Lyman et al. 2004). A main contributor to this is chemotherapy induced pancytopenia^a (CIP) or myelosuppression, a serious side effect of various chemotherapy agents that decrease bone marrow activity. Lowered white blood cell (WBC), red blood cell (RBC), or platelet counts may cause neutropenia (also called leukopenia), anaemia, or thrombocytopenia respectively.

Chemotherapy-induced neutropenia (CIN)

Neutropenia is the most common and potentially serious hematologic toxicity of cancer chemotherapy. Severe neutropenia (SN) or febrile neutropenia (FN) are major risk factors for infection-related morbidity and mortality. Because of this, patients with SN (grade 3 or 4) or FN (neutropenia plus fever) may receive dose reductions and/or delays to their chemotherapy schedule. UK guidelines recommend that chemotherapy is withheld if leucocytes fall below $3000 \times 10^3/\text{mm}^3$ or neutrophils fall below $1.0 \times 10^3/\text{mm}^3$ (Parkar, 2015). This has potential impact on the success of cancer treatment, especially when treatment intent is curative (Aapro, Cameron et al., 2006; Parkar, 2015).

In addition, patients with neutropenia risk serious infection and sepsis, with associated use of hospital accident and emergency departments, hospital admission, and impacts on quality of life (Crawford, Dale et al., 2003). The cost of an episode of FN within the NHS is calculated to be between £2,300 and £3,500 (Mullard, Misra et al., 2014) and may be higher if a patient requires care in a high dependency unit, as in the case of neutropenic sepsis.

^a Pancytopenia is a medical condition which affects the blood cells. It may comprise neutropenia (lowered neutrophils), leukopenia (reduced white blood cells), anaemia (lowered red blood cell count), and thrombocytopenia (lowered platelet counts). The first three conditions are the most dangerous for chemotherapy patients, especially neutropenia as described above.

Granulocyte-colony stimulating factor (G-CSF) is recommended as primary prophylaxis for myelotoxic chemotherapy regimens with a curative/radical intent where the documented risk of FN is 20% or more, or the documented risk is 10-20% and pre-disposing patient risk factors are present. G-CSF is recommended as secondary prophylaxis where occurrence of neutropenia necessitates dose reduction or delays in treatment for patients receiving myelotoxic chemotherapy regimens with curative/radical intent (Parker, 2015). However, G-CSF is not routinely used for all chemotherapy regimens or for all tumour types (such as colorectal or gynaecological cancers), and is not routinely used for treatment in metastatic or late stage cancers (Aapro, Bohlius et al., 2011; Parker, 2015).

Furthermore, a recent audit of two cancer centres in the United Kingdom reported that while adherence to primary G-CSF policy reduced incidence of FN, this did not translate into improved dose intensity, defined as dose reductions and delays. Disruptions to the planned chemotherapy schedule still occurred, caused by non-life threatening toxicities such as myalgia, arthralgia, fatigue and non-neutropenic infections. These were managed by treatment delays until symptomatic improvement, followed by dose reductions in subsequent cycles of chemotherapy (Mullard, Misra et al., 2014).

Chemotherapy-induced anaemia (CIA)

While causes of anaemia in cancer patients are often multi-factorial, anaemia associated with myelosuppressive chemotherapy is reported to affect 19.5% of patients in cycle 1 rising to 46.7% by cycle 5. The National Comprehensive Cancer Network (NCCN) recommends that the following characteristics should prompt evaluation for anaemia (Ludwig, Aapro et al. 2009):

- any patient whose haemoglobin falls below 11 g/dL
- for patients with a high baseline level, a decrease of 2 g/dL during chemotherapy.

CIA can impair quality of life, with patients presenting with fatigue, weakness, impaired cognitive function, respiratory distress and chest pain, and there may be the need for blood transfusion or hospital admission, with associated costs for care (Dranitsaris, Clemons et al., 2005). Incremental improvements in haemoglobin levels have been associated with reduced fatigue and improved quality of life (Wu, Aravind et al., 2009).

Treatments include blood transfusion, iron monitoring and supplementation or rarely, therapy using erythropoietic stimulating agents (ESAs), which carry considerable risks and expense (Rodgers, Becker et al., 2012). The total cost of blood and components per average blood transfusion have been calculated at over £900 (Advancis Surgical, 2013); ESAs have been associated with increased risk of cancer recurrence (Rodgers, Becker et al., 2012).

Chemotherapy-induced thrombocytopenia (CIT)

CIT is another common haematologic toxicity associated with myelosuppressive chemotherapy. Causing bruising and bleeding, it is reported to occur in 10-36% of patients with solid tumours (Wu, Aravind et al., 2009). If severe, it may cause delays, dose reduction or discontinuation of chemotherapy. Severe instances are particularly associated with advanced metastatic cancers. While platelet transfusions are indicated in cases of severe bleeding or if platelets fall below 20, most patients with CIT do not require any treatment other than advice regarding bleeding, observation and monitoring of platelets (Mount Vernon Cancer Network, 2011).

Summary of CIP

These three conditions are associated with considerable effects on morbidity, mortality and costs of care. They may result in chemotherapy dose reductions or treatment delays, with potential impact on clinical outcomes (Lyman, Kuderer et al., 2011). In addition, delays in chemotherapy negatively affect patients' quality of life and may be associated with increased use of healthcare resources (Elting, Rubenstein et al., 2001; Calhoun, Chang et al., 2004). While prophylaxis and interventions exist for more severe levels of CIP, these are not indicated for all types and stages of cancer, nor for lower levels of CIP which may still be associated with reduced quality of life and possible impacts on chemotherapy schedules.

Moxibustion to reduce CIP

This study explores the feasibility of introducing a novel intervention, moxibustion (or moxa), to patients undergoing chemotherapy for breast, gynaecological and colorectal cancers. It will also assess whether this intervention has the potential to:

1. reduce the incidence and/or severity of CIP
2. facilitate completion of chemotherapy according to schedule
3. reduce chemotherapy-induced side effects.

Moxibustion is a component of traditional Chinese acupuncture. It uses the heat generated by the smouldering herb *Artemisia vulgaris* (common name mugwort) to stimulate specific spots on the skin, known as acupuncture points. While it is commonly combined with acupuncture needling, it may also be used on its own, as proposed in this study.

Rationale

Moxibustion may have potential in reducing the risk of CIP. One of the most frequently mentioned uses of moxibustion in the classical Chinese literature is to stimulate the immune system (Wong and Sagar, 2012). A range of types of studies contribute to the developing evidence base to support this claim.

Evidence base – laboratory studies on animals

Laboratory studies using animals have reported improved immune cell function, such as improvement in the production of cytokines and natural killer (NK) cells, after treatment with

moxibustion. Studies using tumour-bearing mice showed that moxibustion down-regulated proliferation of regulatory T cells (Lui et al., 2009); restored the formation rate of altered erythrocytic immunosuppressive factors (Wu et al., 2001); elevated serum IL-2 and IL-12 levels and NK cell activity (Qui et al., 2004); and increased IL-1 β and IL-2 and decreased IL-6 in the cerebral cortex (Pei et al 2010) (cited in Wong, R. and Sagar, S.M., 2012; Zhang, R. and Lao, L., 2012).

Evidence base – randomised controlled trials (RCTs)

Several clinical studies have investigated the effect of moxibustion treatment on chemotherapy-induced leukopenia. A recent systematic review identified six RCTs with a total of 681 patients with a variety of cancers carried out in China (Choi, Lee et al., 2015). Two of the studies, comparing the effects of moxibustion plus chemotherapy with chemotherapy alone, reported higher white blood cell (WBC) and platelet counts in the moxibustion arm than in the control. In addition to increased WBC counts, the remaining four studies also reported reduced side effects of chemotherapy and improved quality of life in the patients receiving moxibustion over controls. The authors of the review concluded that there is a 'low level of evidence' demonstrating the superiority of moxibustion over control in the management of chemotherapy-induced leukopenia (Choi, Lee et al., 2015).

In English language publications, two recent RCTs report promising early results using acupuncture with additional heat treatment. Lu et al (2009) from the Dana Farber Harvard Cancer Centre compared acupuncture plus infrared heat to sham acupuncture in 21 ovarian cancer patients, and reported significantly higher leukocyte values and lower incidence of grade 2-4 leukopenia in the acupuncture arm than in the sham arm. They concluded that clinically relevant trends of higher WBC values during one cycle of chemotherapy suggested a potential myeloprotective effect of acupuncture, and that further research was warranted. Pais et al (2014) measured the effect of acupuncture plus moxibustion (AcuMoxa) with no treatment in 18 colorectal patients undergoing chemotherapy. They reported significantly higher blood counts, including white blood cell (WBC), absolute neutrophil counts (ANC), B cells and NK cells in the AcuMoxa group. Within group analyses revealed increases in WBC, ANC and NK cells in the AcuMoxa group over time, compared with diminishing levels of WBC and NK cells in the control group. They also observed less anxiety and depression in the AcuMoxa arm.

It is postulated that patients with a robust bone-marrow reserve are more likely to complete all scheduled cycles of chemotherapy than those with less reserve (Dranitsaris, Clemons et al., 2005); it may be that moxibustion may help to improve bone-marrow reserves.

Clinical experience and case studies

In the UK, Staebler (2009) evaluated 20 years of clinical experience of teaching helpers of chemotherapy patients to administer daily indirect moxibustion to three pairs of acupuncture points on the back (Bl 17 *ge shu*, Bl 18 *gan shu*, Bl 20 *pi shu*). While observing promising clinical results, Staebler identified factors that prevented an estimated one third of his patients from completing his protocol. These included:

- inability to find a helper to administer home treatment
- dislike of moxa smoke, and
- the time-consuming, inconvenient nature of the intervention.

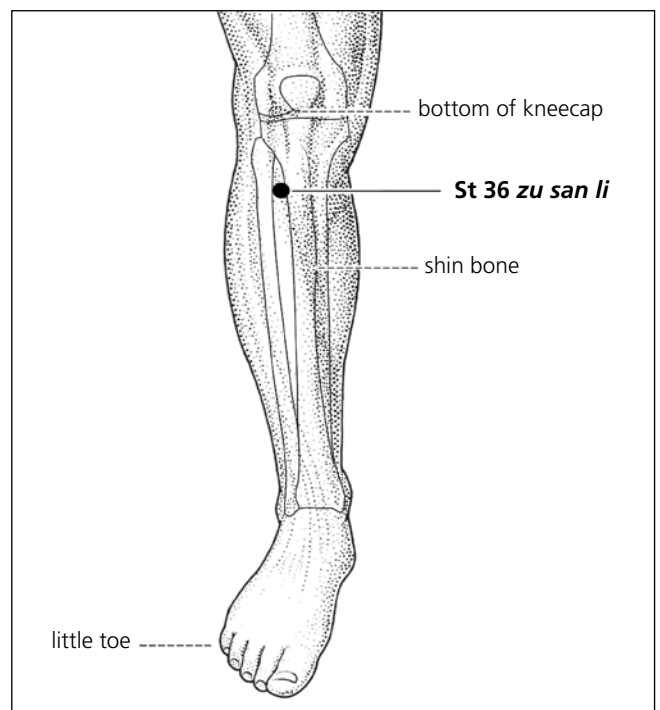


Figure 1: Illustration adapted from 'A Manual of Acupuncture' by Peter Deadman and Mazin Al-Khafaji, with Kevin Baker, and used with their permission.

Davies (2013) simplified Staebler's approach in a case study of patient self-administered indirect moxibustion on St 36 *zu san li*, an acupuncture point on the leg just below the knee. St 36 *zu san li* has been used for centuries in Asian medicine for strengthening the body, improving health, and supporting the immune system. In modern clinical use and in research, it is the most commonly used acupuncture point for immune strengthening and immune regulation (Yim, Lee et al. 2007; Johnston, Sanchez et al., 2011; Wong, R. and Sagar, S.M., 2012). St 36 *zu san li* has been widely used historically and in modern practice and it can be accessed easily by patients for self-treatment.

Mechanisms

The mechanisms of moxibustion are not currently fully established. Moxibustion is thought to influence multiple cortical, subcortical/limbic, and brainstem areas, in part through opioid and monoaminergic neurotransmission (Napadow, 2005, cited in Sagar and Wong, 2012). Another possible mechanism includes an influence on the heat shock proteins, with studies showing that moxibustion upregulated heat shock protein and decreased gastric injury and apoptosis of gastric mucosal cells in rats (Peng, Liu et al., 2012). A third hypothesis is that moxibustion improves the function of immune cells through a neural-hormonal regulatory function: laboratory studies demonstrated higher cellular immune function and increased β -endorphin in the lymphocytes of the spleen in HAC cancer mice. Moxibustion has also been seen to inhibit growth of tumour cells and enhance cellular immune functions via cytokine production (IL-2 or IL-12) and the increase of NK cell activity in tumour bearing mice. (Qiu et al., 2004, cited in Sagar and Wong, 2012).

Building the evidence base

Literature and systematic reviews confirm the need for further evidence to support using moxibustion to reduce CIP (Bovey, 2009; Lee, Choi et al., 2010; Kim, Chae et al., 2011; Zhang, Lin et al., 2013) and Choi et al (2015) concluded that 'future RCTs appear to be warranted'. We aim to build on the platform established by Staebler and Davies, in the first study of the effects of self-administered moxibustion on CIP conducted in a Western oncology setting.

This study will enable systematic monitoring of:

- patient adherence to the moxibustion protocol
- blood counts
- variations to planned chemotherapy schedules.

It will also enable assessment of the impact on chemotherapy-related toxicities and quality of life. The study will provide a first measure of the feasibility and potential effectiveness of using this approach. Data collected will provide the basis for developing further research, such as a randomised controlled trial comparing moxibustion plus chemotherapy with chemotherapy alone for chemotherapy patients for whom G-CSF is not indicated. There may also be the potential for future studies to compare moxibustion with G-CSF for early disease.

Evolving an approach for use in the NHS

We have worked with Staebler to modify his protocol in the following ways, to make it easier to implement in a NHS setting:

1. Using St 36 *zu san li*: we have chosen to use a single pair of points (bilateral St 36 *zu san li*), which is located on the leg below the knee, rather than the three pairs of points on the back (Bl 17 *ge shu*, Bl 18 *gan shu*, Bl 20 *pi shu*) as used by Staebler. This enables the patient to administer the protocol themselves, without requiring a helper.
2. Using a single point bilaterally: this reduces the time to complete the protocol from 30 minutes to less than ten minutes. As per Staebler's protocol, the moxa stick will be held approximately 3-4 centimetres above the point until the skin reddens slightly, and we recommend that this is three minutes on each point.
3. Using smokeless moxibustion sticks: this minimises smoke and aroma, increasing acceptability to patients and their housemates.

Cost of moxibustion treatment

Treatment with moxibustion is a very low cost intervention. A typical smokeless moxa stick costs approximately £1 with a potential burn time of one hour, with an estimated cost of less than £5 per cycle of chemotherapy. Enabling patients to self-administer moxibustion keeps treatment costs to a minimum, by avoiding reliance on an acupuncturist. In this study, we plan to provide continuing support to participants by providing:

- access to a video demonstrating the procedure (made available as a YouTube video online or DVD, according to participant preference)
- regular text or email reminders (according to participant preference) to encourage their continued practice of self-administered moxibustion for the duration of their chemotherapy treatment.

METHODS/DESIGN

Study design

The study design is shown in Figure 2. It is an uncontrolled, observational single-arm, single-site feasibility study using mixed methods. Quantitative data will be collected to monitor: adherence to daily moxibustion, blood counts, completion of chemotherapy according to schedule, and impact on chemotherapy side effects and quality of life. Qualitative data will be collected on the acceptability of self-administered moxibustion to patients (focus groups) and oncology health professionals (interviews).

Approvals

This study is conducted in compliance with the Helsinki Declaration (World Medical Association, 2013) and is badged with the National Cancer Research Network (UKCRN; Study ID: 19916). NHS Research Ethics Committee (REC) approval has been granted (London – Fulham REC, ref: 15/LO/1571) and local R&D approval has been obtained.

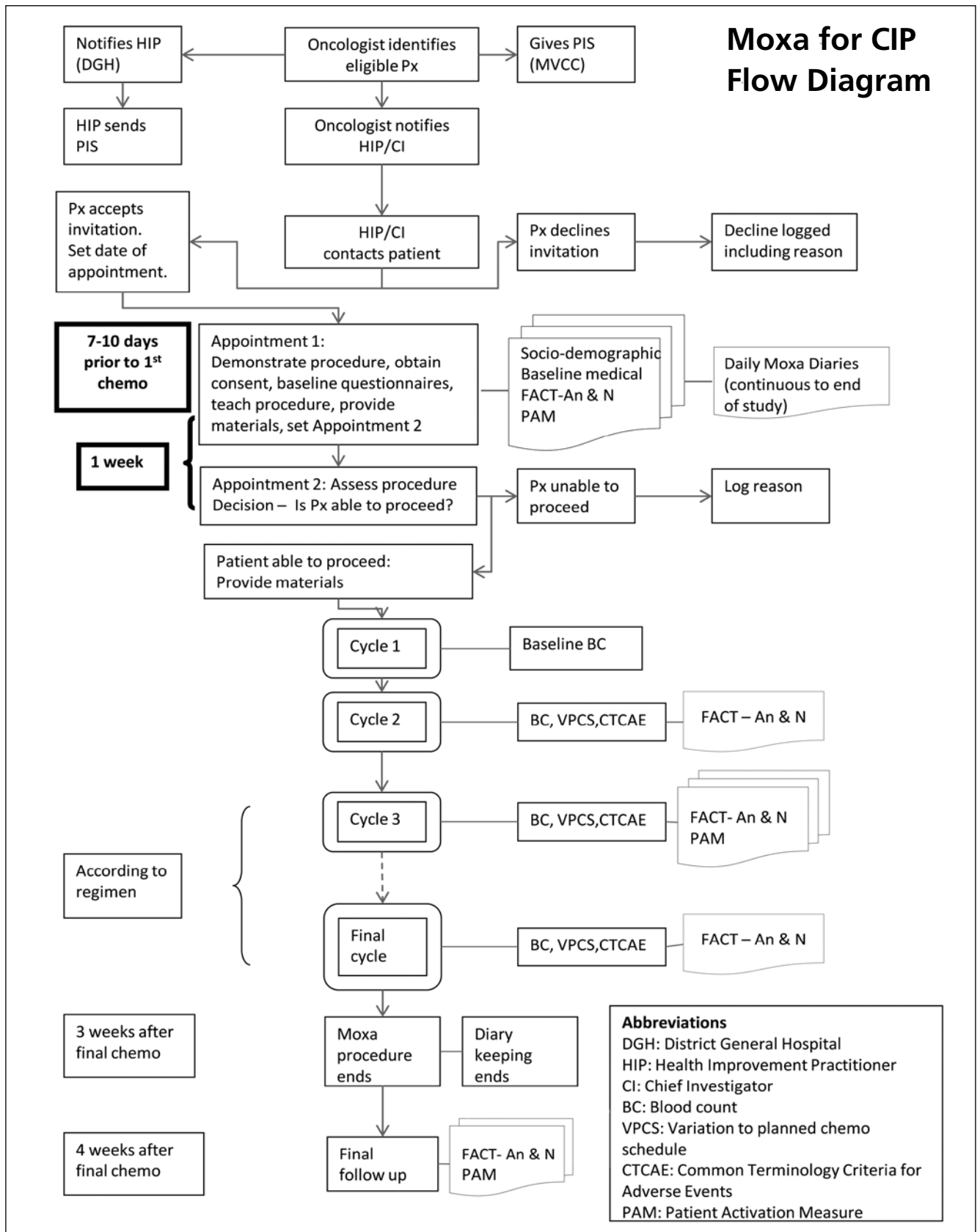


Figure 2: Study design

Aims and objectives

The primary aim of this study is to assess the feasibility of teaching cancer patients undergoing chemotherapy in the NHS to self-administer daily indirect moxibustion to *St 36 zu san li* to reduce pancytopenia, thus integrating the intervention into a typical chemotherapy schedule. Secondary aims are to:

- obtain a first measure for the effectiveness of using moxibustion to reduce pancytopenia (especially neutropenia and anaemia)
- obtain a first measure of whether this intervention facilitates completion of chemotherapy according to planned schedule
- collect preliminary data to investigate claims that patients using moxibustion experience fewer chemotherapy related toxicities (Lee, Choi et al., 2010)
- obtain a first measure for the impact of moxibustion on quality of life
- assess the acceptability of this approach to a) patients and b) oncology medical professionals
- monitor adverse events of moxibustion, data that is usually lacking in moxibustion studies (Park, Lee et al., 2010).

Inclusion/exclusion criteria

Inclusion criteria

Patients:

- female or male, aged 18 to 75
- with breast, gynaecologic, and colorectal cancer who are prescribed:
 - radical or adjuvant chemotherapy in the early disease setting, or
 - first or second line chemotherapy if in the metastatic setting
- about to commence a course of chemotherapy for which G-CSF is not routinely indicated
- with a life expectancy of more than six months
- with blood cell counts within the normal range
- with calculated creatinine levels of ≥ 50 ml/min
- English speaking
- able to understand instructions for self-administration of moxibustion and carry out the procedure
- able to give informed consent.

Exclusion criteria

Patients:

- having a haematological cancer diagnosis
- prescribed a chemotherapy regimen for which G-CSF is indicated
- having third or fourth line chemotherapy
- having metastatic bone cancer
- who have concomitant severe medical problems preventing participation
- with cognitive impairment that would impact participant's ability to safely administer self-moxibustion
- having renal dysfunction
- with lymphoedema in the lower body.

Recruitment and consent

We aim to recruit 25 participants, at a rate of 5 per month, over five months.

Recruitment processes

1. Many cancer patients are first seen by a 'visiting' oncologist from Mount Vernon Cancer Centre (MVCC) at a District General Hospital (DGH), where a decision is made to offer chemotherapy. The oncologist at the DGH will inform the patient about the study, and obtain their verbal consent to pass their details to the health improvement practitioner (HIP), who will subsequently contact them to invite their involvement in the study and supply a participant information sheet (PIS).
2. Patients who first meet their oncologist at MVCC will be given a PIS by a member of their direct care team and the role of the HIP will be explained. With the patient's verbal consent, the member of the direct care team will inform the HIP, who will then make contact with the patient by phone and/or email to invite them to discuss participation in the study.

Obtaining written consent

After the patient has received the PIS, the HIP will contact the patient. If interested, the patient will be invited to attend an intake interview. The HIP will demonstrate the technique and answer questions. If the patient is still interested, they will be asked to provide written consent by completing the study consent form.

The timings will be as follows. Patients will be contacted by the HIP one to two days after they have received the PIS. They will be invited to attend an intake interview within a further one to two days. Patients will probably need to decide during the intake

interview whether to consent in order to allow seven to ten days to practise the procedure before their chemotherapy starts.

Intervention

The moxa protocol

The moxa protocol consists of daily application of moxibustion to bilateral St 36 *zu san li* for three minutes on each point (total six minutes). Participants will be expected to:

- commence moxa treatment as early as possible before starting chemotherapy (ideally seven to ten days)
- administer moxa daily throughout the full chemotherapy regimen
- continue for three weeks after the end of chemotherapy.

Teaching the protocol

Up to ten days before commencing their first cycle of chemotherapy participants will be taught self- moxibustion. The HIP will set up two meetings with each participant (who may be accompanied by a helper, if wished). In the first meeting, lasting about one hour, the HIP will:

- explain the concept of moxibustion
- demonstrate the procedure
- answer any questions
- obtain written consent
- administer baseline questionnaires
- teach how to light, use and extinguish moxa safely
- teach how to locate St 36 *zu san li*
- mark the point with surgical pen
- discuss the necessity of daily application of moxa on St 36 bilaterally for three minutes on each point
- demonstrate how to log treatment in the daily moxa diary
- provide a moxa pack for one week of treatment
- provide access to the support materials (video and instruction leaflet, see below)
- arrange an appointment for one week later.

Up to three days before the first chemotherapy treatment, participants will attend Meeting Two. During this meeting, lasting about 45 minutes, the HIP will:

- ask the participant to demonstrate their handling and application of the moxa
- ensure that the participant is able to carry out the procedure correctly
- assess the participant's ability to proceed with the study
- deal with any questions or concerns
- provide the moxa supplies to cover the period until the next set of questionnaires will be administered (see below).

Moxa supplies and support materials

Participants will be furnished with the necessary supplies, including smokeless moxa sticks, a lighter, an extinguisher for the moxa, a butane refill for the lighter, a surgical marking pen, and a timer.

We will provide the participant with the following support mechanisms:

- written and illustrated instructions describing all aspects of the process, including instructions on what to do in case of a burn. This leaflet, *A Patient's Guide: Using moxa to reduce the side effects of chemotherapy*, was designed by the award-winning information team at the LJMC. It is available at http://www.ljmc.org/pi_series/pi81_moxa.pdf
- access to a YouTube video demonstrating how to locate St 36 *zu san li*, and how to use moxa. A DVD will be given to participants who prefer not to use the internet. This can be accessed at http://www.ljmc.org/2_research/projects/moxa.html
- regular reminders to carry out the moxa procedure will be sent out by text or email
- a phone number to contact for difficulties relating to the self-administration of moxibustion.

Participant information will make clear the importance of adhering to the information given to them about seeking help quickly if neutropenia is suspected.

Administration of questionnaires and supply of materials

The HIP will meet each participant when they attend for each chemotherapy session, to:

- answer any questions that have arisen
- top up the supply of moxa, if necessary
- administer relevant questionnaires
- collect the daily moxa diary for the previous period, and give the participant a new daily moxa diary to cover the period until the next chemotherapy treatment.

Measures

We will measure outcomes as outlined in Table 1.

Participants will be monitored from their commencement on the study (ideally seven to ten days prior to their first chemotherapy treatment) until one month after the last chemotherapy treatment (Figure 1).

Sociodemographics

Sociodemographic variables include age, marital status, educational qualification, work status, country of birth, ethnic background, car and home ownership, dependents.

Baseline medical

These variables include participant weight, height, body mass index (BMI), cancer diagnosis, tumour staging, date of diagnosis, surgical history, planned chemotherapy protocol and agents, comorbid illnesses, current medications for pre-existing conditions, ECOG (Eastern Cooperative Oncology Group) status.

Primary outcome: adherence to moxa protocol

Participants will complete a daily moxa diary, to log their adherence to the daily protocol. They will be asked also to log any days they miss, and give reasons why. The daily moxa diary was designed in house, and is not a validated measure.

Secondary outcomes

Blood counts: Blood counts will be collected from the participants' medical notes to monitor incidents of CIP.

Variation to planned chemotherapy schedule: Any delays in chemotherapy schedule and the reasons why will be collected from the participants' medical records.

Chemotherapy related toxicities: Data will be collected using the common terminology criteria for adverse events (CTCAE), which is the standard form used in the chemotherapy suite to record information about any toxicities experienced by the patient (such as fatigue, vomiting).

Table 1: Outcome measures

Outcome	Measure	Interval
Adherence to moxa regimen	Daily moxa diary	Daily – from seven to ten days prior to first chemotherapy treatment until one month after last chemotherapy treatment.
Blood counts (BC), specifically haemoglobin, white blood cells, neutrophils, and platelets	Full blood count	According to chemo schedule (usually fortnightly for colorectal, three weekly for breast and gynaecologic cancers)
Variation to planned chemo schedule (VPCS)	Patient records	As above
Chemotherapy related toxicities	CTCAE (common terminology criteria for adverse events)	Prior to each cycle of chemotherapy
Quality of life	FACT-N and FACT-An	Baseline; Cycle 2; Cycle 3; Cycle 6 (or final treatment); one month after end of chemo
Patient self-management	Patient Activation Measure (PAM)	Baseline, Cycle 3, four weeks after final chemo
Safety	Incident count from participant report, moxa diaries and CTCAE	Ongoing
Concurrent therapies	Use of therapies that affect blood cell counts, including steroids, iron supplements and other dietary supplements, blood and platelet transfusions	Ongoing

Health related quality of life: The study will seek to identify changes in quality of life, to help with hypothesis generation for future studies. For this, we have chosen validated tools designed by the Functional Assessment of Chronic Illness Therapy (FACIT) organization (<http://www.facit.org/FACITOrg>) comprising the FACT-G, FACT-N, and FACT-An scales. The Functional Assessment of Cancer Therapy – General (FACT-G) is a 27-item compilation of general questions covering physical, social/family, emotional and functional wellbeing. It is the generic, core questionnaire of the FACIT measurement system, and is appropriate for use with patients with any form of cancer (Cella, Tulsky et al., 1993). It can be used in conjunction with symptom specific measures, of which we have chosen the FACT-N and FACT-An. FACT-N is a 19-item neutropenia subscale designed to capture symptoms and impact on health related quality of life related to neutropenia (Wagner, Beaumont et al. 2008). FACT-An is a 20-item questionnaire assessing fatigue and anaemia-related concerns in people with cancer (Yellen, Cella et al., 1997).

Patient self-management: Patients with a high level of activation are likely to engage in positive health behaviours and participate in managing their health conditions more effectively (Hibbard, 2004). We will use the Patient Activation Measure (PAM) to explore whether it is possible to identify patients who will be most likely to follow a daily healthcare regimen.

Safety: The safety of moxibustion is under-reported in the literature (Park, Lee et al., 2010). We will monitor and record all incidents affecting safety, including allergies, burns, and other accidents.

Concurrent therapies: We will record whether participants are taking or having therapies that affect blood cell counts, including steroids, iron supplements and other dietary supplements, blood and platelet transfusions.

Statistical considerations

Primary aim

We will use the daily moxa diaries to assess adherence to the procedure. In particular:

- the total number of times a participant actually administered moxa relative to the total number of days on the study
- the mean number of times per week the participants administer the moxa
- any changes over time in the number of administrations per week.

As this feasibility study is looking at a form of self-management, we also will measure patient activation, using the Patient Activation Measure (PAM). We will seek to identify if there is

a relationship between a person's concept of themselves as an active manager of their health and healthcare, and their adherence to the daily moxa procedure (Hibbard, 2004).

Secondary aims

To inform the design of possible future studies, we will also collect descriptive data as follows:

- frequency counts of eligible patients approached, accepting and declining invitation to participate (acceptance)
- frequency counts of occurrences of neutropenia ($< 1 \times 10^3/\text{mm}^3$) and severe neutropenia ($< 0.5 \times 10^3/\text{mm}^3$) three weeks after first and subsequent cycles of chemotherapy for breast and gynae cancers, and at two week intervals for colorectal patients
- frequency counts of occurrence of anaemia
- frequency counts of occurrence of delay or dose reduction of second and subsequent cycles of chemotherapy
- occurrence of chemotherapy related toxicities
- analysis of daily moxa diaries and participants' verbal reports of adverse events of moxibustion (safety)
- monitoring quality of life, combining FACT-N and FACT-An to identify changes in quality of life, to help with hypothesis generation for future studies.

Statistical analysis

Data will be analysed using the current versions of SPSS and Excel, and presented in tables and charts as appropriate to the data. Participants who drop out will not be replaced, as our primary aim is to investigate adherence. The data collected while they are on the study will be analysed. We will also ask any participants who drop out of the study for their consent to continue to use their clinical data, so we can follow up and monitor the blood counts and toxicities after stopping moxa treatment.

Qualitative data

Qualitative data on acceptability of the intervention will be collected in two focus groups with participants, and with interviews with oncology healthcare professionals. These will take place at the end of the recruitment and clinical phase of the study.

DISCUSSION

This study is the first study to assess the use of self-administration of moxibustion by chemotherapy patients in an oncology setting. Using moxibustion in the prevention of chemotherapy-induced pancytopenia is a novel, non-pharmaceutical, non-invasive approach for which there are only case reports in the English language. It is essential to build the evidence base for this

approach, and to develop the data and research experience required in order to apply to major funders (such as the National Institute of Health Research (NIHR), the main funder for NHS based research). This study builds on the clinical precedents established by Staebler and Davies (Staebler, 2009; Davies, 2013).

The design is a feasibility study, appropriate to initial exploratory research in this area. It uses mixed research methods (qualitative and quantitative) and explores an innovative intervention (teaching chemotherapy patients to self-administer moxibustion). This feasibility study provides the basis for subsequent larger studies, particularly future randomised controlled trials.

It will contribute to the developing evidence base for moxibustion. It will also compile patient feedback and experiences of self-administered moxibustion as well as investigating the acceptability of this novel approach to oncology health professionals.

By measuring patient activation, we hope to be able to develop a means of identifying future patients for whom this form of self-care will be appropriate. If successful, this form of treatment may be a valuable and low cost form of prophylaxis for CIP. There are some limitations that should be considered. The majority of cancer patients attending for chemotherapy at Mount Vernon Cancer Centre are first seen at their district general hospital. This may pose difficulties in identifying suitable participants, obtaining consent, and training them in the seven

to ten day period before chemotherapy starts. In this feasibility study, we will recruit interested patients up to and including the first cycle of chemotherapy, and monitor the result. Another challenge to the design of this study is the stand-alone nature of the intervention. In all the clinical reports and research to date, patients have attended for moxibustion treatment by a trained professional and/or receive ongoing care by their acupuncturist. In this study, participants will be self-administering outside of the context of regular acupuncture and moxibustion treatment, and we will monitor the acceptability of this.

CONCLUSION

Cancer is forecast to affect one in two of the population by 2030. Now is the time to lay the foundations for exploring the potential role that self-administered moxibustion can play in improving treatment for cancer patients undergoing chemotherapy.

Staebler (2009) wrote that he hoped that 'one day the research community in the West will take a closer look at what daily moxibustion can offer in the treatment of chemotherapy-induced bone marrow depression'.

Funding

The clinical phase of this study is made possible by funding from the British Acupuncture Council. Set-up activities have been covered by funding from the Supportive Oncology Research Team at the Lynda Jackson Macmillan Centre, and by Research Capacity Funding from East & North Hertfordshire NHS Trust.

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