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Original Research Article

AL study- traditional Chinese medicine combination *Astragalus membranaceus* and *Ligustrum lucidum* in people with advanced malignancy: research protocol for an open labelled pilot study

Bhagwant K. Sekhon[1]*, Philip Beale[2], Janette L. Vardy[3], Kellie A. Charles[4], Ross D. Brown[5], Henry Liang[6], Stephen J. Clarke[7], Andrew J. McLachlan[1]

[1]Faculty of Pharmacy and Centre for Education and Research on Ageing, University of Sydney and Concord Hospital, Sydney, NSW, Australia
[2]Concord Cancer Centre, [3]Sydney Medical School, Concord Hospital Sydney, University of Sydney, Sydney, NSW, Australia
[4]Discipline of Pharmacology, Sydney Medical School, University of Sydney, Sydney, NSW, Australia
[5]Haematology, Sydney Cancer Centre, Royal Prince Alfred Hospital Sydney Medical School, Sydney, NSW, Australia
[6]Chinese Medicine Program, School of Science and Health, University of Western Sydney, Sydney, Australia
[7]Director Area Cancer Services (Northern Sydney Cancer Centre), Kolling Institute of Medical Research and the Bill Walsh Cancer Research Laboratory, Royal North Shore Hospital and University of Sydney, Sydney, NSW, Australia

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***Correspondence:**
Ms. Bhagwant Kaur Sekhon,
E-mail: bhagwant.sekhon@sydney.edu.au

ABSTRACT

Background: AL is a traditional Chinese medicine (TCM) combination commonly used as an adaptogen to improve energy levels, immunity and quality of life in those suffering from chronic diseases such as cancer. While the combination *Astragalus membranaceus* and *Ligustrum lucidum* (AL) has been investigated in China as an adjunct to standard anticancer therapies in numerous clinical studies of variable quality reported in the Chinese literature, independent assessment of its effects on safety, tolerability and efficacy are lacking. Our objectives are to determine the safety and tolerability of AL and investigate its effects on inflammation, quality of life and immunity in people with advanced malignancy in the Australian healthcare setting.
Methods: The AL study is a prospectively registered, open labelled pilot multi-centre study investigating AL in people with advanced malignancy. Inclusion criteria include participants with recurrent or metastatic cancer who are not undergoing chemotherapy or palliative chemotherapy. All participants (n=25) will receive 6 capsules of AL twice daily (equivalent to 25g raw herb) for 12 weeks. Follow up consultations will monitor safety, tolerability, quality of life, immune function and adverse events. Participants will be assessed at baseline and at weeks 3, 6, 9 and 12. The primary outcome will determine the effect of AL on safety and tolerability. Secondary outcomes will include inflammation, quality of life, immune function, disease status and survival. Appropriate statistical analysis will be conducted on the pilot study data. Potential associations will be investigated where relevant.
Conclusions: This study will firstly establish the safety and tolerability of this TCM combination 'AL' in people with advanced malignancy in the Australian healthcare system and provide important information regarding its effect on markers that may affect survival as well as explore changes in quality of life and immune function. The impact of this research may allow the design of future studies integrating AL with standard therapy for people with advanced malignancy.

Keywords: Advanced cancer, Traditional Chinese medicine, *Astragalus*, *Ligustrum*, Pilot study

INTRODUCTION

Traditional Chinese medicine (TCM) is commonly employed as an adjunct to standard anti-cancer treatment in China and other countries.[1,2] An analysis of a population based cohort of 1065 women with breast cancer in Shanghai demonstrated that 98% of patients had used at least one form of complementary and alternative medicine (CAM) therapy after diagnosis, and that TCM was used by 86.7% of patients.[3] In Australia, the use of CAM in cancer patients ranges from 17-65%.[4-6] The increasing trend in cancer patient use mirrors those of the general population and a recent study estimated 79% of cancer survivors had used at least one form of CAM in the last 12 months.[7] Additionally, 21% of non-English speaking Chinese Americans reported using CAM, particularly Chinese herbal medicine, acupuncture and Chinese massage for treating cancer related pain.[8] *Astragalus membranaceus* and *Ligustrum lucidum* (AL) are foundational herbs known as adaptogens which purport to normalise the body's functions towards wellbeing and are commonly prescribed in many TCM formulations to combat various stressors such as cancer.[9]

With over 20 years of pre-clinical and clinical research, AL is being used by many people with cancer (often in conjunction with various chemotherapy regimens) for its claimed benefits on immune function, "energy levels", and to improve general well-being.[10] Research suggests that one way in which these herbal medicines elicit positive effects is by stimulating the immune system often supressed in people living with cancer. In a meta-analysis on 34 randomized studies that combined *Astragalus*- based Chinese herbal medicine with platinum based chemotherapy (versus platinum-based chemotherapy alone), 12 studies reported reduced risk of death at 12 months and 30 studies showed improvement in tumour response.[10] Similarly in a more recent meta-analysis, 20 trials (n=1520 patients) investigating *Astragalus*- based Chinese herbal medicine with platinum based chemotherapy (versus platinum-based chemotherapy alone) on survival at 12 months resulted in a pooled risk ratio (RR) of 0.65, 95% CI 0.54 to 0.79 with the effect being consistent at 24 and 36 months; and 57 trials indicated a pooled RR of 1.35; 95% CI 1.26 to 1.44 in favour of herbal treatment.[11] A randomised study investigating the effects of AL tonic capsules with chemotherapy compared to chemotherapy alone on the quality of life of patients with oral and maxillofacial squamous carcinoma found significant increases in Karnofsky performance status (KPS).[12] Another randomised study investigating the effects of a daily *Astragalus* intravenous injection and mitomycin c, vinblastine and cisplatin chemotherapy (MVP protocol), compared to chemotherapy alone in patients with advanced NSCLC found that after 2-3 cycles of treatment there was a significant increase in disease free survival, median survival and 1 year survival ($p<0.05$) as well as quality of life ($p<0.01$) in the treated group, compared to control.[13] While there is some indication AL may be useful as a potential adjunct to standard anticancer therapy, high quality evidence is needed to determine its safety, tolerability and efficacy. As patients with advanced malignancy have few effective treatment options, this open labelled pilot study firstly aims to determine the safety and tolerability of AL in the Australian healthcare setting in people who are no longer undergoing chemotherapy.

METHODS

The AL study is an open-labelled, multi-centre pilot study examining the effect of AL in people with advanced malignancy who are either ineligible for, or who have declined palliative chemotherapy. Ethics approval has been granted by the Sydney Local Health District Human Research Ethics Committee at Concord Hospital (HREC/14/CRGH/139 CH62/6/2014-114). The study has been registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12615001203549) and the study protocol is in accordance with the SPIRIT statement.[14]

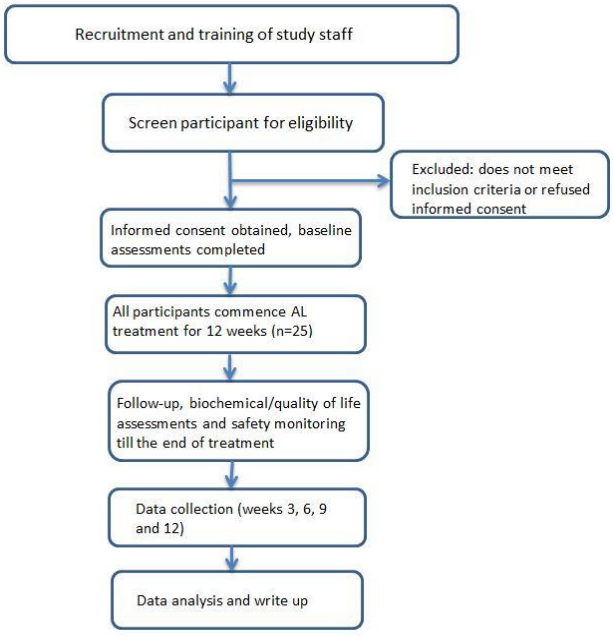

Figure 1: AL protocol flowchart.

AL study design

Participants and recruitment

Participants will be recruited from Medical Oncology clinics at Chris O'Brien Life House, Royal Prince Alfred Hospital, Royal North Shore Hospital, and Concord Cancer Centre at Concord Repatriation General Hospital via their medical oncologist. A member of the study team will screen the participant against the eligibility criteria.

Eligible participants will meet all of the following criteria: diagnosis of recurrent or metastatic cancer; accessible for treatment and follow up; aged 18 years or older; able to swallow capsules whole; and sufficient understanding of the English language to give written informed consent and to complete the study assessments and self-reported questionnaires.

Participants will be excluded if they meet any of the following criteria: currently undergoing chemotherapy including palliative chemotherapy; ECOG status ≥ 3; life expectancy ≤12 weeks; inadequate haematopoetic function (WBC $<3.0\times10^9$/L; ANC $<1.5\times10^9$/L, platelets $<100\times10^9$/dL), or renal function (eGFR <50 mL/min/1.73m^2); inadequate hepatic function (either AST/ALT >2.5×ULN, or >5×ULN in case of liver metastases, or bilirubin >1.5×ULN); any major pre-existing psychiatric history or dementia that (in the view of the investigator) would interfere with the ability to provide informed consent and/or compliance with study procedures; pregnant or lactating women; cerebral or leptomeningeal metastases that are unstable in spite of cranial radiotherapy and/or stereotactic radiosurgery; serious intercurrent medical illness including (but not restricted to) HIV, active infection, unstable angina, severe heart failure, or ongoing surgical complications; major surgery within 2 weeks prior to study commencement; concurrent radiotherapy; clinical evidence of current or impending bowel obstruction; reluctance or inability to cease other Traditional Chinese or other herbal, homeopathic or naturopathic medicines at least a week prior to trial commencement; concurrent use of immune-modulators; documented allergy to study compounds; and participating in (or planning to participate in) trials of other pharmacological agents during their time on the AL study.

Study treatment

The study treatment will consist of commercially available AL capsules known as "Zhenqi Fuzheng Capsules (ZFC)" extracted by an herbal pharmaceutical company in China (Gansu Fuzheng Pharmaceutical Technology Co. Ltd). This product has been registered by China State Drug Administration as a prescribed medicine (Z62020987). All participants will receive 6 AL capsules twice daily (equivalent to 25g raw herb) for 12 weeks.

Data collection

Data collection will be carried out during clinic visits by a member of the study team at baseline and at weeks 3, 6, 9 and 12. Data will be collected despite participant compliance.

Primary outcomes

The primary outcome will be the proportion of participants to experience adverse events (safety) and complete the study (tolerability).

Secondary outcomes

Inflammation measured at baseline and weeks 6 and 12 will be assessed by changes in the neutrophil-lymphocyte ratio, C-reactive protein and albumin.[15-17] Modulation of immune function measured at baseline and at weeks 6 and 12 will be assessed by changes in general T-cells, regulatory T-cells, cytotoxic T-cells, pro-inflammatory T-helper 17 cells, natural killer cells and dendritic cells by flow cytometry. The functional assessment of cancer therapy questionnaires-fatigue (FACT-F and FACT-G), measured at baseline and at weeks 6 and 12, rated as an average over the last 7 days will measure quality of life in general and specifically fatigue.[18,19] The general health questionnaire (GHQ12) measured at baseline and at weeks 6 and 12, rated as an average over the last few weeks will assess symptoms of anxiety and depression.[20]

Other data collection

Concomitant medications will be collected at baseline and weeks 6 and 12. Details of adverse events will be collected at weeks 6 and 12. Participants will be asked to complete a toxicity diary daily that will be compared against adverse events recorded during the study and other assessments. While there are relatively few reported adverse effects in the literature (Chinese language), when administered with many chemotherapy regimens in a variety of tumour types, AL would be unlikely to cause significant harm in the absence of concurrent therapy. However, possible adverse events include minor gastro intestinal upset, skin eruption and itching, hypertension, headache, dizziness and insomnia. Any serious adverse events defined as life threatening, resulting in death, hospitalisation, or significant disability will be reported immediately to the Data Monitoring Safety Board and research ethics committee.

Adherence to study medication will be assessed by self-report and by counting the returned medication as compared to the prescribed dose during clinic visits at week 6 and at the end of the study at week 12.

Data integrity and analysis

Data integrity will be maintained by regularly reviewing the data for missing data and errors and any inconsistencies will be resolved. Descriptive statistics will summarise participant data. If the data is continuous, secondary outcome assessment will be based on t-tests or the non-parametric equivalent test if the data is not normally distributed. If the secondary endpoint is categorical, contingency tables, proportions and frequencies will be used to summarise the results. On-sample proportion, chi-square, McNemar and Fisher's exact tests will be used where appropriate. Exact p-values and 95% confidence intervals will be reported for all notable results, and plots and tabled data will be used to further describe the variables of interest.

Investigation of potential association between the primary endpoint and the baseline factors of age, gender and tumour type will be undertaken using regression techniques. Linear transformations of skewed data will be performed as appropriate.

For all statistical tests, a p value of 0.05 will be considered statistically significant. However, since many secondary analyses will be conducted some tests may appear statistically significant due to chance, even if no association exists. These analyses will therefore be considered exploratory and are not powered to draw definitive conclusions.

Sample size

A sample size of 25 participants has been selected in order to adequately assess the safety and tolerability of AL based on comparable studies conducted in oncology.[21] Discussions with the clinicians involved strongly suggest this is feasible in a timely manner. Additionally, the results of the pilot study will inform a larger randomised study with a comparator treatment arm.

Modification of the protocol

Any changes to the protocol that may affect the design or conduct of the study will require a formal protocol amendment. All amendments will be agreed upon by the study investigators and ethics approval will be sought prior to its implementation. Once approval has been obtained, the changes will be communicated to all parties involved including members of the study team, doctors and participants.

DISCUSSION

AL is currently used as an adjunct to HIV antiretroviral therapy and platinum-based chemotherapy regimens in China.[11,22] Many studies published in the Chinese language have reported positive outcomes in terms of quality of life and immune function in association with AL when combined with standard therapy. For example, a recent study has found that *Astragalus* polysaccharide intravenous injection with vinorelbine and cisplatin, significantly improved the overall quality of life (p=0.003) in patients with advanced NSCLC compared to chemotherapy alone, but did not affect tumour response or survival.[23] Another randomised study in 120 cancer patients receiving chemotherapy alone or with adjuvant *Astragalus* injection found less decrease in peripheral white blood cells and platelet count; a significant decrease in CD8 cells with an increase in the CD4/8 ratio, IgG and IgM levels as well as elevated KPS in the *Astragalus* group compared to the control.[24] However, despite these positive findings, at present there is limited, verifiable high quality evidence on the effect of AL in patients with cancer available and accessible in the English language to inform their treatment in the Australian healthcare setting. This paper presents the design and rationale for a prospective open-labelled, multi-centre, pilot study evaluating the safety and tolerability of AL and its effects on inflammation, immunity, quality of life and survival in people with advanced malignancy. If AL is found to be safe and there is a trend for improvement in quality of life and immune function while reducing inflammation, these results will be instrumental in the design and conduct of future studies investigating herbal medicine combinations with chemotherapy, starting with a larger randomised control trial comparing AL with standard treatment. In addition, the results of these studies will better inform clinicians and patients as there is at present a paucity of independent clinical data on safety and efficacy, despite their use by a significant number of patients.

We anticipate recruitment to commence in the second half of 2016, with data collection completed by end of 2017.

In summary, the results of the AL study conducted in the Australian healthcare setting will help clarify the validity of the current evidence on the safety and tolerability of AL in people with cancer and provide preliminary efficacy data In addition, the AL pilot study concept looking at preliminary inflammatory markers will present a simple and effective screening platform for investigating medicinal agents of herbal or plant origin with adaptogenic potential combined with standard therapy.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of the Sydney Local Health District Human Research Ethics Committee at Concord Hospital (HREC/14/CRGH/139 CH62/6/2014-114)

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