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Short communication

Is clarithromycin a potential treatment for cachexia in people with lung cancer? A feasibility study

Sarah Awan[a], Vincent Crosby[a], Vanessa Potter[b], Ivo Hennig[b], David Baldwin[c], Mehluli Ndlovu[d], Sharon Paradine[e], Andrew Wilcock[b,*]

[a] Department of Palliative Care, Nottingham University Hospitals NHS Trust, Nottingham, NG5 1PB, UK
[b] Department of Clinical Oncology, Nottingham University Hospitals NHS Trust, Nottingham, NG5 1PB, UK
[c] Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham, NG5 1PB, UK
[d] Nottingham Health Science Partners, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, UK
[e] Consumer representative, c/o National Cancer Research Institute, Angel Building, 407, St. John Street, London, EC1V 4AD, UK

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ABSTRACT

Clarithromycin may improve cachexia and survival in non-small cell lung cancer (NSCLC), but adequately controlled data are lacking. This study was undertaken primarily to inform the feasibility and scale of a phase III trial. Eligible consenting patients with stage IV NSCLC and cachexia were to be randomized to receive either clarithromycin 250 mg twice daily or placebo for eight weeks. Aspects of trial feasibility recorded included numbers eligible, approached and recruited, together with adherence and completion of treatment and assessments. Over 6 months, none of 125 patients identified fulfilled the entry criteria. The commonest reasons for ineligibility were the use of an excluded concurrent drug (45, 36%), brain metastases (22, 18%), poor performance status (21, 17%) and current chemotherapy (15, 12%). A phase III trial of clarithromycin using these entry criteria is not feasible in this setting. Other macrolides that have a lower risk of a drug–drug interaction may be more practical to pursue.

1. Introduction

Cachexia is common in lung cancer and is associated with increased morbidity and reduced survival [1–4]. No standard treatment exists and cachexia is a major unmet need [5,6]. Clarithromycin (CLM) is reported to preserve body weight, physical independence and increase survival in patients with lung cancer [7,8]. The mechanism may relate to its anti-inflammatory effect as inflammation appears a key contributor to cachexia [9–11]. CLM also has immunomodulatory and anti-cancer effects [12–14], thought to explain benefit in some haematological cancers [15].

CLM is potentially an inexpensive and widely available cachexia treatment. However, no RCTs have been undertaken. Further, CLM interacts with multiple drugs, which increases the risk of toxicity; prolongation of the QT interval is a particular concern because it predisposes to life-threatening cardiac arrhythmia. Thus, we have undertaken a randomized, double-blind, placebo-controlled, feasibility study to obtain data to ensure that a phase III study, which takes such safety concerns into account, is viable, practical, uses appropriate outcome measures and is sufficiently powered.

2. Materials and methods

For additional details see Supplementary Appendix A.

2.1. Participants

Patients were identified from thoracic oncology clinics at a University hospital. Inclusion criteria included age ≥18 years, stage IV non-small cell lung cancer (NSCLC), an estimated prognosis of ≥3 months, ≥4 weeks following any 1st or 2nd-line palliative chemotherapy, along with the presence of cachexia (based on any of: weight loss >5% over past 6 months; body mass index <20 kg/m^2 and weight loss >2%; appendicular skeletal muscle index consistent with sarcopenia and weight loss >2%), systemic inflammation (C-reactive protein >10 mg/L), and adequate hepatic and renal function.

Exclusion criteria included poor prognostic features (Eastern Cooperative Oncology Group (ECOG) performance status ≥3, little or no food intake, weight loss >10% in 1 month or >20% in total), active infection requiring antibiotics, inability to accurately

* Corresponding author.
E-mail address: andrew.wilcock@nottingham.ac.uk (A. Wilcock).

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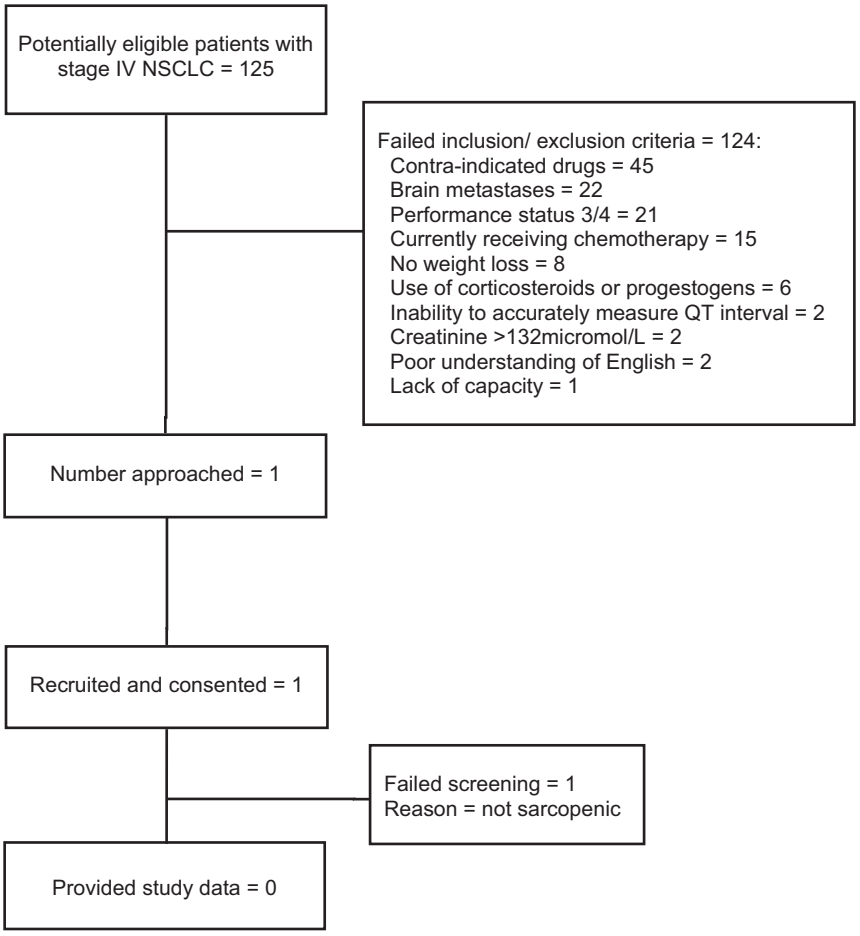

Fig. 1. Patient flow chart.

measure QT interval, features predisposing to cardiac arrhythmia (QTc >450 ms (male) or 470 ms (female), history of ventricular arrhythmia, severe cardiac insufficiency), hypokalaemia, hypomagnesemia, concurrent use of drugs with the potential to increase QT interval or enhance other toxicities of CLM (see Supplementary Appendix B), use of corticosteroids or progestogens within the last 4 weeks, brain metastases and *Clostridium difficile* infection.

2.2. Study procedures

Following written informed consent and confirmation of eligibility, patients were to be randomized to receive encapsulated CLM 250 mg or matching placebo, taken by mouth twice daily for eight weeks. The study received approvals from Medicines and Healthcare Regulatory Agency (03057/0063/001-0001), National Research Ethics Service Committee East Midlands – Nottingham (14/EM/1281) and was on the EU clinical trials register (2014-004873-18).

2.3. End points and assessments

The primary objective was to obtain data on rates of eligibility, recruitment (over 12 months), data collection and study completion. Secondary objectives were to obtain preliminary data on the (a) tolerability of CLM (based on adherence to treatment); (b) safety of CLM (based on continual monitoring of toxicity, ECGs to detect prolongation of the QT interval) and (c) effect of CLM on patient-centred outcomes of lean body mass, physical function, quality of life and systemic inflammation.

2.4. Statistical analysis

A formal power calculation is not appropriate for a feasibility study; the sample size reflected the recruitment rate from a large cancer centre, an important aspect of feasibility under exploration. Mostly descriptive statistics were used. Appropriate parametric/non-parametric statistics would have been used in an exploratory context to compare changes from baseline in patient-centred outcomes.

3. Results

3.1. Aspects of feasibility

Over 6 months, of the 125 patients identified, only one was recruited with a weight loss >2% and BMI >20 kg/m^2; however, they failed to meet the criteria for sarcopenia on DEXA scan. As a consequence, the decision was taken to close the study.

The commonest reasons for ineligibility were the use of an excluded concurrent drug (45, 36%), brain metastases (22, 18%), poor performance status (21, 17%) and current chemotherapy (15, 12%); for a full list see Fig. 1.