SHORT COMMUNICATION

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

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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 250mg 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.

Key words: cachexia, clarithromycin, macrolide antibiotics, non-small cell lung cancer

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 2.

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 <20kg/m^2 and weight loss >2%; appendicular skeletal muscle index consistent with sarcopenia and weight loss >2%), systemic inflammation (C-reactive protein >10mg/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 measure QT interval, features predisposing to cardiac arrhythmia (QTc >450milliseconds (male) or 470milliseconds (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 1), 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 250mg 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

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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, but 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.

One patient was receiving two excluded concurrent drugs, the remainder one of 17 different kinds, the most common being amlodipine, oxycodone and zopiclone (Table 1).

4. **Discussion**

Our failure to recruit suggests that a phase III double-blind, placebo-controlled study of clarithromycin using these entry criteria is not feasible. None of the 125 patients screened met the eligibility criteria. For just under half, this was because of brain metastases, poor performance status or concurrent chemotherapy. However, the single most common reason, affecting about one-third, was the concurrent use of a drug with the potential to interact with CLM to a degree that is known to be, or likely to be, clinically significant. This represents an extensive list of 100 drugs, of which 17 were used by the 45 patients so excluded. It could be argued that we were overly cautious, given that such considerations are unlikely to be

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strictly adhered to in clinical practice. However, this mostly reflects the short-term use of CLM as an antimicrobial. In proposing its long-term use as a cachexia treatment, we consider additional caution appropriate, particularly given concerns about prolongation of the QT interval and the increased risk of ventricular arrhythmias and sudden cardiac death observed in patients receiving CLM (and other macrolides) [16]. Previous studies of CLM for cancer cachexia predate the emergence of these safety concerns [7, 8].

Given the preliminary reports of impressive benefits of CLM in cancer cachexia [7, 8], rather than abandon this area completely, the potential exists to explore the feasibility of using alternate macrolide antimicrobials. For example, although azithromycin has no 'track record' in cachexia, it also has immunomodulatory properties [17, 18], is used long-term [19, 20], and has a lower risk of a drug-drug interaction, such that only 10 of our patients would have been excluded on this basis. A formal feasibility study is required to confirm improved recruitment and to explore other aspects of the study still untested in our patient group.

In conclusion, a phase III double-blind, placebo-controlled study of CLM for cachexia using these entry criteria is not feasible. The use of other macrolides with a lower risk of a drug-drug interaction may be feasible, but requires formal evaluation.

Conflict of interest

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among patients with non-cystic fibrosis bronchiectasis: the BAT randomized

controlled trial, JAMA 309 (2013) 1251–1259.

Table 1

Concurrent drugs used resulting in exclusion.

Drug	Number of patients
Amlodipine	10
Oxycodone	9
Zopiclone	4
Atorvastatin	3
Clopidogrel	3
Warfarin	3
Citalopram	2
Venlafaxine	2
Verapamil	2
Buprenorphine	1
Colchicine	1
Diltiazem	1
Eplerenone	1
Felodipine	1
Fentanyl	1
Gliclazide	1
Tamsulosin	1

Fig. 1. Trial flow diagram.