Updated protocol and guest participant results from the ACCeRT clinical study

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Abstract

Introduction: Cancer cachexia is a condition often seen at diagnosis, throughout chemotherapeutic treatments and in end stage Non-Small Cell Lung Cancer patients. These patients often experience a shorter life-expectancy and deterioration in performance status and reduced quality of life. New multi-targeted regimens are required to be tested in this population to address these issues.
Materials and methods: The ACCeRT study is an open label, prospective, randomised controlled feasibility study investigating the use of eicosapentaenoic acid and COX-2 inhibitor (celecoxib) versus eicosapentaenoic acid, COX-2 inhibitor (celecoxib), progressive resistance training followed by ingestion of essential amino acids high in leucine in Non-Small Cell Lung Cancer cachectic patients. The study protocol was published in November 2011. Due to study participants and study team preferences a number of changes were made. Firstly, a change from a bolus drink containing 20 g of essential amino acids to an encapsulated form in divided doses over three days. Secondly, a change in leg strength analysis from utilising a leg/back dynamometry to a customised chair with a load cell testing extension isometric force. Thirdly, study drug dose reductions were now permitted. Fourthly, addition of two study sites which allowed participants to attend progressive resistance training sessions in their local area. Finally, a change in inclusion criteria to include participants that had received any first-line anti-cancer treatment. A guest participant was invited onto the study in April 2012, followed by the first study participant in June 2012.
Results: The guest participant showed trends in efficacy in a number of outcomes; stable fat free mass in the context of decreasing total body weight, with stable FAACT-PWB, MFSI-SF physical, and WHOQOL-BREF QOL scores at week 20, all during documented disease progression now termed refractory cachexia. There were no treatment or exercise-related adverse events.
Conclusion: Publishing feasibility study protocols allows transparency in study interventions and assessments. The above ACCeRT regimen stabilised fat free mass and a number of physical/performance indicators and QOL in the guest participant.

Keywords: Cancer cachexia, EPA, COX-2 inhibitor, PRT and EAA

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Introduction

While the definition of cancer cachexia has developed over the years (1-3), it is commonly referred to as a "multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment", and now incorporates the development of the stages of cachexia including pre-cachexia, cachexia and refractory cachexia (4). Notably, the incidence of cachexia is tumour type and site dependent, with Non-Small Cell Lung Cancer (NSCLC) patients having documented rates of 61% (5, 6). Of clinical importance, cachexia is estimated to be present in up to 80% of cancer patients at time of death (3).

Over the last few decades, a number of pharmacological agents and methods of support have been investigated to address the primary areas of cancer cachexia (7). Firstly, addressing anorexia via appetite stimulation, corticosteroids in the form of oral methylprednisolone, prednisolone and dexamethasone (8-11), progestinal agents in the form of medroxyprogesterone acetate and megestrol acetate (12-14), cannabinoids in the form of dronabinol (15), thalidomide (16), and more recently L-carnitine (17). Secondly, addressing alterations in energy and substrate metabolism in the form of melatonin (18), and ghrelin (19). Thirdly, addressing skeletal muscle loss via targeting the anabolic and catabolic pathways in the form of enobosarm (20), espindolol (21, 22), and bimagrumab (23). Lastly, addressing inflammation in the form of clazakizumab (24), and xilonix (MABp1) (25).

Research addressing cancer cachexia has also included multi-targeted approaches with the combination of agents (26-28). The combination of the anti-cachectic agent eicosapentaenoic acid (EPA) and the COX-2 (cyclo-oxygenase-2) inhibitor celecoxib has been tested in a small study of NSCLC patients with some benefit (29). While the use of progressive resistance training (PRT) followed by the oral ingestion of essential amino acids (EAA), has been reported to provide a potent anabolic stimulus on skeletal muscle and appears acceptable in older adults and other cancer groups (30-33).

Therefore, as a companion study to our previous works (34), the aim of this randomised controlled feasibility study was to evaluate the acceptability of a multi-targeted approach encompassing a PRT protocol and nutritional supplementation (20 g EAA high in leucine) for lung cancer patients experiencing cancer cachexia.

Materials and methods

Trial design and changes

Auckland's **C**ancer **C**achexia **e**valuating **R**esistance **T**raining study (**ACCeRT**) is an open label, prospective, randomised controlled feasibility study. The study was registered by Australian New Zealand Clinical Trials (ACTRN12611000870954). Participants were randomised in a 1:2 ratio into one of the following two treatment arms: **A)** EPA and COX-2 inhibitor (international best supportive care); or **B)** EPA, COX-2 inhibitor and PRT (2 sessions per week) plus 20 g EAA high in leucine (treatment group). The study planned for 21 participants to be enrolled for a 20 week investigation period. No treatment arm crossover was permitted during the study. All participants completing the 20 week study, irrespective of which arm they were randomised to, were offered to continue or receive study medication/training sessions under compassionate use.

The following PRT exercise prescription was developed for this new population and was instigated in a non-linear method. PRT sessions were supervised by a clinical exercise physiologist. The planned PRT was broken into five × 4 week phases that were periodised across the 20 weeks progressing in volume, intensity and complexity of exercise. Resistance was

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provided via use of elasticated exercise bands (Theraband, USA), dumbbells or bodyweight. If the participant presented with disease-related symptoms, orthopaedic issues and/or bone metastasis, a conservative approach was taken to minimise risk and potential discomfort. This was achieved via a reduction of exercise loading and/or use of an alternative exercise to suit the participant's needs. As indicated, participant's heart rate and peripheral capillary oxygen saturation (SpO2) levels were monitored during exercise sessions.

During phase 1, PRT consisted of fundamental upper and lower body resistance exercises in a seated position. Upper body exercises included iso-lateral chest press and row movements. Lower body exercises included iso-lateral knee flexion and extension. Exercises performed were prescribed at 1 set of up to 8 repetitions, with initial intensity set at a Rate of Perceived Exertion (RPE) of "very light" to allow for familiarisation of the movements, which was to then be increased to an RPE of "light". With phase 2 the above prescribed exercises were continued with the addition of a dumbbell bicep curl. Exercise volume was increased by adding a second set and intensity was increased to an RPE of "somewhat hard". For phase 3, partial squat exercises were introduced and the upper body exercises were performed in a standing position. Exercise volume and intensity was set to be maintained. For phase 4, the exercise prescription was maintained however, with intensity was increased to an RPE of "hard". During phase 5, the PRT intensity was maintained. Upon completion of phase 5 (20 weeks), compassionate PRT was offered with no further changes to the PRT prescription.

Primary endpoint

To determine the acceptability of a multi-targeted approach of supportive care in cachectic NSCLC participants. Assessed by the analysis of a patient rated Likert scored questionnaire asking 10 questions on the acceptability of the above multi-targeted approach, both at week 12 and week 20/end of trial (EOT) visit.

Secondary endpoints

To assess the trends in efficacy and safety of the above multi-targeted approach of supportive care in cachectic NSCLC participants.

Efficacy was assessed by comparison between the two groups using the following data;

1. Body composition assessed by bioelectrical impedance analysis (BIA).
2. 3T Magnetic Resonance Imaging (MRI) total quadriceps muscle volume.
3. Serum proinflammatory cytokine profiles analysing the 'classic cachexia cytokines' Interleukin-1β, Interleukin-6 and Tumour Necrosis Factor-α (IL-1β, IL-6 and TNF-α).
4. Hand-grip strength assessed by hand grip dynamometry of the dominant hand.
5. Leg strength assessed by isometric back/leg dynamometry (PE018 Back Dynamometer, Access Health), or from amended protocol by isometric force by customised chair and load cell.
6. Compliance results analysed as percentage of total taken of study medication and attendance of study sessions.
7. QOL and fatigue assessed by the following questionnaires; The Functional Assessment of Anorexia/Cachexia Therapy (FAACT physical well-being subscale (PWS)). The Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). World Health Organization Quality of Life-Brief (WHOQOL-BREF) overall QOL.
8. Prognostic score assessed by laboratory values of albumin and C-reactive protein (CRP) incorporated into the Glasgow Prognostic Score (GPS).

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9. Performance status assessed by Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and Karnofsky Score (KS).

Safety was assessed by comparison between the two groups using the number of serious adverse events (SAEs) and changes on electrocardiogram (ECG) assessments.

Trial changes

Reasons for performing a feasibility study include testing the integrity of the components of the study in terms of treatments, follow-up assessments, testing questionnaires as well as gaining rates of consent, recruitment and retention, and selecting the primary outcome measure for the main study (35). The primary outcome in the ACCeRT study was the clinical acceptability of the multi-targeted approach in this specific population. This included the schedule of study intervention/medication and study visits, along with gaining experience around secondary outcomes in terms of the technical aspects of leg strength analysis and 3T MRI muscle analysis (36).

Encapsulation

The bolus ingestion of 20 g of EAA within a 250 ml non-caffeinated drink was tested and it was discovered that it had poor palatability. It was decided before the study commenced to change to an encapsulated form. Therefore, all participants received the total dose of 20 g of EAA high in leucine capsules (500 mg per '0' sized gelatin capsule) for a total of 40 capsules per each PRT session over three days commencing 1 hour after PRT as per schedule (Table 1).

Table 1. Essential amino acid schedule utilised within the ACCeRT study.

EAA (g)	Number of capsules	Time point
4 g	8	1 hour post exercise
4 g	8	Evening post exercise
3 g	6	Day 2 - afternoon
3 g	6	Day 2 - evening
3 g	6	Day 3 - afternoon
3 g	6	Day 3 - evening

EAA; Essential Amino Acids.

Leg strength dynamometry

Participants' leg strength analysis was to be performed at all study visits, and assessed by back/leg dynamometry of both legs. It was identified that it was difficult to maintain set joint angles during maximal isometric contraction in this population while using the back/leg dynamometer, and its use by non-exercise physiologist staff and participants had commented on the unacceptability of this equipment. In addition, there was safety concerns around its use in participants with spinal bone metastases, which had not been previously investigated; therefore, the presence of bone metastases was an exclusion for this study assessment.

A change was made to utilise a customised extension rig (chair) with a 1kN (kilo Newton) load cell in series to measure isometric force. Maximum voluntary contraction (MVC) was carried out by clinical exercise physiologists, assessed over a period of 10 seconds with considerable verbal encouragement. Contractions were repeated three times at 1 minute intervals.

Participants sat in the customised rig (chair) and velcro straps were placed across the pelvis/waist, thighs and chest to minimise movement from joints other than the knee. The starting knee position was set to 90° flexion, with participants crossing their arms across the chest during the testing. Isometric force was assessed for either the right or left knee extensor (quadriceps

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femoris) muscle group. A comfortable padded cuff was placed around the lower leg, just above the malleolus, and attached to a chain in series with the load cell (Figure 1). The load cell output was amplified (RM044, Applied Measurement, Victoria, Australia) and sampled at 200 Hz (200 samples per second) by a 64-bit A–D converter (PCI-6035E, National Instruments, TX, USA) connected to a personal computer. Load cell results gained initially in LabVIEW Measurement data (Labview, National Instruments, TX, USA) presented in Millivolts, kg and Newtons. The results were then converted into EXCEL software for analysis and the highest of the three attempts at each study visit recorded as the MVC.



Figure 1. Pictures of a volunteer undergoing leg strength testing.

Study drug dose reductions

Some participants expressed that they found taking the study drug medication (EPA, COX-2 inhibitor, and EAA) unpalatable or just too large in quantity with other concomitant medication. It was decided to allow participants to dose reduce the quantity of study medication.

Locations

Cancer and Blood Services at Auckland City Hospital was the main referring centre for cancer patients. Geographically it covers North, East, South and West Auckland patients. Potential participants had turned the study down due to travelling distance and time to this location. Participants were now able to attend the PRT sessions at a centre nearest their location.

Inclusion criteria

The original inclusion criteria included participants that had 'recently completed first-line platinum-based chemotherapy'. During recruitment it was identified that firstly, a percentage of patients were advised and received a non-platinum chemotherapy regimen, or radiotherapy alone to palliate symptoms. Secondly, publicly funded gefitinib was accessible to New Zealand patients (July 2012), along with private access to erlotinib or the compassionate use of the ALK inhibitor - crizotinib. The protocol was amended to include all participants who had received at least a first line anti-cancer treatment which could include either surgery, chemotherapy, radiotherapy and/or a targeted therapy.
All the above amendments were deemed as being in line with the aims of carrying out a feasibility study.

Guest participant

The ACCeRT study was utilising a number of new techniques, new members of the research team, along with a new research location. It was decided to invite a participant onto the study as a 'guest' to identify any potential scheduling and technique issues prior to recruiting to the main study. The guest participant was a

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New Zealand European 78 year old male, with stage IV squamous lung cancer of the left upper lobe (bone, adrenal, bilateral lung) diagnosed 875 days (2 years, 4 months and 24 days) before study entry. He had received four previous lines of treatment. Baseline weight 92.5 kg reduced to 90.5 kg (-2.6% over 3 months). Total days on study 20 weeks (148 days), plus compassionate use up to 32 weeks (236 days). Died 60 weeks (420 days) after enrolment. Received RT to the left chest during the last week on study 20 Gy in 5# during PRT 39, 40 and 41. Then commenced fifth line single-agent vinorelbine chemotherapy, for 2 cycles, with cycle 1, day 1 during PRT 63/64, and cycle 1 day 8 during PRT 65/66. Response evaluation criteria in solid tumours (RECIST) data, showed continued disease progression as detected by chest-x-ray in May and August 2012, and was later confirmed by CT in November 2012.

Results

Primary outcome

The guest participant completed the acceptability questionnaire both at week 12 and week 20/EOT study visits. EPA and COX-2 inhibitor (celecoxib) acceptability and palatability was scored high at 5 'strongly agree' for both visits. PRT sessions and EAA acceptability/palatability also scored high at 5 for both study visits. The guest participant also scored 5 for the final question on wishing highly to continue with all the medication and exercise sessions.

Compliance data showed EPA and COX-2 inhibitor (celecoxib) 100% compliance, with PRT attendance of 100% up to weeks 12 and 20 with a missed PRT session up to week 32. EAA compliance of 100%, 98.3% and 98.9% at weeks 12, 20 and 32 (missed two doses 1 x 8 g, 1 x 6 g = 14 g) respectively. These results indicate the high acceptability of the allocated multi-targeted regimen in the context of progressing NSCLC by the completion of a patient rated questionnaire and the compliance/attendance levels of the study medication and training sessions. The combination of EPA, COX-2 inhibitor (celecoxib), PRT sessions and EAA, were acceptable to the guest participant at the stated doses and sessions. The guest participant completed the 20 week study period and chose to continue with compassionate use of study medication and PRT sessions.

Secondary outcomes

A minor loss of BIA FFM from baseline was seen at weeks 12 and 20 with an overall change of -0.3 kg (-0.5%) at week 20 (Table 2). Total body weight change at week 12 of +0.1 kg (+0.1%), and of -4.5 kg (-5%) at week 20. This indicates stable weight, then weight loss returned at week 20. Interestingly, this data indicates that while total body weight had decreased by almost 5% at week 20, this was limited to only -0.5% in FFM. From week 20 to week 32/3 month compassionate use (CU) shows the progressing loss of both FFM and weight of -4.9 kg (-8.8%) and -11.2 kg (-12.3%) respectively. Data shows the MRI total quadriceps muscle volume change from baseline to week 20/EOT of -178 cm^3 (-10.4%), indicating loss of total quadriceps muscle volume. The change from baseline in IL-6 levels of -0.86 pg/ml at week 12 and an increase of +4.16 pg/ml at week 20. With a corresponding increase in TNF-α levels of +2.87 pg/ml at week 12 and +1.73 pg/ml at week 20. Both levels of IL-6 and TNF-α remained relatively stable over 20 weeks, with decreased levels at week 32/3 month CU indicating a reduction in the proinflammatory cytokines. Hand-grip strength data demonstrates a change from baseline of -10 kg (-30.3%) at week 12, indicating loss of muscle strength. This loss remained stable with -12 kg (-36.4%) at week 20. Leg strength data shows an increase in strength. This suggests that the PRT sessions did not assist in maintaining hand-grip strength, but possibly increased leg strength.

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Albumin level data shows decreasing levels of -4 g/L at week 12 and -7 g/L at week 20. This indicates nutritional stability up to week 12 then decreasing nutrition at week 20. CRP level data shows increasing levels of +25 g/L at week 12 and +65 g/L at week 20, indicating progressing inflammation over study period to week 20. Both levels of albumin and CRP decreased at week 32/3 month CU indicating a slight reduction in nutrition status, and decreasing inflammation. This could be attributed to the guest participant receiving single-agent vinorelbine chemotherapy during this period.

Table 2. Guest participant results.

	Baseline	Week 12	Week 20	Week 32 (3 month CU)
BIA				
FFM (kg)	55.8	54.7	55.5	50.9
Total Body Weight (kg)	90.8	90.9	86.3	79.6
MRI				
Total quadriceps muscle volume (cm^3)	1705		1527	
Proinflammatory cytokines				
IL-6 (pg/ml)	11.56	10.7	15.72	9.97
TNF-α (pg/ml)	17.19	20.06	18.92	11.37
Strength				
Hand grip (kg)	33	23	21	
Leg (Newtons)	941.8		1069.3	
Prognostic				
Albumin (g/L)	40	36	33	32
CRP (mg/L)	30	55	95	83
GPS	1	1	2	1
Performance status				
ECOG-PS (KS)	1 (80)	1 (80)	1 (80)	1 (75)

BIA; Bioelectrical Impedance Analysis, FFM; Fat Free Mass, MRI; Magnetic Resonance Imaging, IL-6; Interleukin-6, TNF-α; Tumour Necrosis Factor-alpha, CRP; C-Reactive Protein, GPS; Glasgow Prognostic Score, ECOG-PS; Eastern Cooperative Oncology Group Performance Status, KS; Karnofsky Performance Status, CU; Compassionate Use.

FAACT-PWB data showed change of +2 and +1, with MFSI-SF physical scale a change of -1 and -1, and WHOQOL-BREF overall QOL score change of +0 and -2 at weeks 12 and week 20 respectively. All indicating that the guest participant's physical well-being and QOL remained stable.

Table 3 indicates that the guest participant either achieved or over-achieved the planned progression during phase 1 to IV, but then under-achieved during phase V, due to symptoms of progressive disease. The guest participant then achieved an adapted program during PRT from weeks 41 to 68. Compassionate PRT was discontinued at week 33/PRT 68 due to SAE from chemotherapy.

For safety, all participants received omeprazole 20 mg o.d. and received a 12-lead ECG at baseline, week 12 and week 20. The guest participant was already prescribed diltiazem 120 mg o.d, and no significant changes were seen in ECG assessments throughout the study. One SAE was experienced while receiving compassionate use; grade 3 febrile neutropenia (neutropenia grade 4) and grade 2 constipation due to vinorelbine chemotherapy and infected dog bite.

Discussion

ACCeRT is the first to utilise a multi-targeted regimen in the refractory cancer population and a comparison with other research studies cannot be made at this point. Similar studies that have implemented a multi-targeted approach include the randomised phase II feasibility trial of lung and pancreatic cancer patients

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undergoing cycles III and IV of standard chemotherapy, randomised to standard care or oral nutritional supplements, anti-inflammatory (celecoxib) and home-based aerobic (twice weekly) and resistance training (three time weekly) known as the Pre-MENAC study (37). This has been followed by the phase III MENAC study which randomises patients undergoing chemotherapy to either standard care or oral nutritional supplements, anti-inflammatory medication (ibuprofen) and home-based self-assisted exercise program, currently recruiting (38). Both of these trials are targeting early cachexia. It has been stated that the combination of physical inactivity, inflammation and poor nutritional status may prevent the reversal of weight and muscle loss, and that any intervention would be unlikely to see a reversal of the cachexia related symptoms within the last 90 days of life (39). The above guest participant achieved 32 weeks on the ACCeRT regimen and, survived for a further 28 weeks post-end of compassionate use. These results indicate that patients may benefit from a multi-targeted approach in cachexia symptom management even during the late/refractory stage.

Table 3. Guest participant progressive resistance training results.

	Phase I Weeks 1 to 4	Phase II Weeks 5 to 8	Phase III Weeks 9 to 12	Phase IV Weeks 13 to 16	Phase V Weeks 17 to 20	Phase VI Weeks 21 to 24	Phase VII Weeks 25 to 28	Phase VIII Weeks 29 to 32
	PRT 1 to 8	PRT 9 to 16	PRT 17 to 24	PRT 25 to 32	PRT 33 to 40	PRT 41 to 48	PRT 49 to 56	PRT 57 to 64
PLANNED	'very light' to 'light' BORG 8-11	'somewhat hard' BORG 12-13		'hard' BORG 14-15		'somewhat hard' BORG 12-13		
UPPER	achieved BORG 11	over-achieved BORG 13	achieved BORG 13	over-achieved BORG 15	under-achieved BORG 13	achieved BORG 13	achieved BORG 13	achieved BORG 13
LOWER	over-achieved BORG 12	over-achieved BORG 13	achieved BORG 13	over-achieved BORG 15	under-achieved BORG 13	achieved BORG 13	achieved BORG 13	achieved BORG 13

PRT; Progressive Resistance Training.

Conclusions

The ACCeRT study protocol received minor amendments responding to both study participants and research team members to allow optimization of the planned study protocol. The guest participant results showed acceptability to the multi-targeted schedule with high levels rated in both the questionnaire and high compliance with study medication and PRT session attendance. These amendments were utilized within the main study, which has completed recruitment and full study results in press. Collectively, the results for the guest participant demonstrate efficacy in stabilising FFM in the context of decreasing total body weight, potentially via a muscle protein-sparing effect. Furthermore, stable FAACT-PWB, MFSI-SF physical and WHOQOL-BREF QOL scores were reported at week 20, all during documented disease progression now termed refractory cachexia. The current findings provide preliminary support for the potential health-related benefits associated with combined PRT and EAA ingestion, however caution is warranted in the interpretation of the results as they are limited to one participant.

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Authors' contribution

ESR conceived the study. ESR, RDM, and JWLK participated in the design of the study. JS was responsible for the statistical planning of the trial. ESR and RDM wrote the study protocol. RS provided study medical assistance, GMS and MRW provided progressive resistance program development. SPB provided nutritional advice. BA provided study oversight. All authors read and approved the final manuscript.

Conflict of interest

SPB is a consultant to Musashi, Vitaco Health Australia Pty Ltd. All other authors declare that they have no competing interests.

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Ethics approval and consent to participate

This study has been approved by the appropriate ethics committee (Health and Disability Ethics Committees; NTY/11/06/064) and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave their written informed consent prior to their inclusion in the study. The guest participant gave their written informed consent for publication.

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