

Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer

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Abstract

Background Combinations of exercise and nutritional interventions might improve the functional prognosis for cachectic cancer patients. However, high attrition and poor compliance with interventions limit their efficacy. We aimed to test the feasibility of the early induction of new multimodal interventions specific for elderly patients with advanced cancer Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) programme.

Methods This was a multicentre prospective single-arm study. We recruited 30 of 46 screened patients aged ≥ 70 years scheduled to receive first-line chemotherapy for newly diagnosed, advanced pancreatic, or non-small-cell lung cancer. Physical activity was measured using pedometers/accelerometer (Lifecorder[®], Suzuken Co., Ltd., Japan). An 8 week educational intervention comprised three exercise and three nutritional sessions. The exercise interventions combined home-based low-intensity resistance training and counselling to promote physical activity. Nutritional interventions included standard nutritional counselling and instruction on how to manage symptoms that interfere with patient's appetite and oral intake. Supplements rich in branched-chain amino acids (Inner Power[®], Otsuka Pharmaceutical Co., Ltd., Japan) were provided. The primary endpoint of the study was feasibility, which was defined as the proportion of patients attending ≥ 4 of six sessions. Secondary endpoints included compliance and safety.

Results The median patient age was 75 years (range, 70–84). Twelve patients (40%) were cachectic at baseline. Twenty-nine patients attended ≥ 4 of the six planned sessions (96.7%, 95% confidence interval, 83.3 to 99.4). One patient dropped out due to deteriorating health status. The median proportion of days of compliance with supplement consumption and exercise performance were 99% and 91%, respectively. Adverse events possibly related to the NEXTAC programme were observed in five patients and included muscle pain (Grade 1 in two patients), arthralgia (Grade 1 in one patient), dyspnoea on exertion (Grade 1 in one patient), and plantar aponeurosis (Grade 1 in one patient).

Conclusions The early induction of multimodal interventions showed excellent compliance and safety in elderly patients with newly diagnosed pancreatic and non-small-cell lung cancer receiving concurrent chemotherapy. We are now conducting a randomized phase II study to measure the impact of these interventions on functional prognosis.

Keywords Non-small-cell lung cancer; Pancreatic cancer; Elderly; Cancer cachexia; Multimodal intervention; Physical activity

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Introduction

Maintenance of skeletal muscle mass and physical function during systemic chemotherapy is often challenging in advanced cancer patients.^{1–3} The situation is even worse in the elderly cancer patients because they potentially have age-related sarcopenia,⁴ malnutrition,⁵ and high risk for falls.⁶ We previously reported that skeletal muscle depletion with functional decline starts early in chemotherapy for elderly patients with newly diagnosed advanced non-small-cell lung cancer (NSCLC).⁷ Approximately half the patients experienced clinically significant decline in walking ability during the first 3 months. Additionally, the majority of patients had cancer cachexia and easily developed disability during their cancer courses.⁸ Although several clinical trials of investigational agents reported their positive effect on appetite or lean body mass in cachectic cancer patients, there was no improvement as compared with the control group in physical functions including handgrip strength^{9–11} or 6 min walking distance.¹¹ One possible reason may be a lack of concurrent nutritional and exercise interventions.¹² However, there is no standard multimodal intervention combining with these investigational agents. Previous multimodal intervention trials in patients with advanced cancer had poor recruitment, poor compliance, and minimal impact on physical function¹³ or quality of life.¹⁴ The burden of multiple assessments, extra effort, and time spent in the intervention may have decreased compliance. Inclusion of patients in later phases of the cancer course may further limit feasibility and efficacy of the interventions.

In this study, we evaluated the feasibility of early induction of a new multimodal intervention specifically for elderly patients with advanced NSCLC or pancreatic cancer, which are two major cancer types with high cachectic potential.

Materials and methods

Patient selection

The Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC)—one study is designed as a national, prospective, multicentre, single-arm study to assess the feasibility and safety of the early introduction of non-pharmacological multimodal interventions for elderly patients with advanced cancer receiving chemotherapy. Patients were recruited from Kyoto Prefectural University of Medicine, National Cancer Center Hospital East, Niigata Cancer Center Hospital, and Shizuoka Cancer Center. The eligibility criteria were as follows: (i) histologically and/or cytologically proven advanced (locally advanced or metastatic) NSCLC or pancreatic cancer; (ii) age ≥ 70 years, with a scheduled first-line systemic chemotherapy course; (iii) no previous systemic chemotherapy

except for adjuvant chemotherapy or chemoradiation completed >6 months before study entry; (iv) Eastern Cooperative Oncology Group performance status (PS) of 0–1 and Barthel Index of >90 points; (v) having at least one source of social support (family members or friends) who could monitor safety and compliance with the intervention throughout the 8 week study period; and (vi) the ability to ambulate, read, and respond to questions without assistance. Patients were excluded if they had an indication for curative radiotherapy or surgery, a severe psychiatric disorder, an active infectious disease, unstable cardiac disease, or untreated symptomatic brain or bone metastases that prevented safe assessments or interventions. Written informed consent was obtained after the diagnosis was confirmed and ≥ 7 days before the initiation of the first chemotherapy. The study was approved by the institutional review board of each institution.

Assessment timing

The assessment schedule and contents are summarized in Table 1. Baseline assessments were performed during the time between study entry and initiation of chemotherapy (T1 point). Subsequent assessments were at 4 ± 2 (T2 point) and 8 ± 2 (T3 point) weeks after the T1 point.

Nutritional assessment

At each time point, body weight (kg) was measured and the body mass index (BMI) (kg/m^2) was calculated. The registered dietitians assessed nutritional status using the full version of the Mini Nutritional Assessment[®]. Caloric and protein intakes were estimated using 2 day diet diaries or the 24 h recall method.^{15,16} Routine checklist for nutrition impact symptoms (NIS)¹⁵ included anorexia, nausea, vomiting, constipation, diarrhoea, fatigue, oral mucositis, taste and smell disturbance, early satiety, masticatory disturbance, and dysphagia. Patients were instructed to complete a diet diary and record their weight, amount of food intake, and NIS (see Supporting Information, Data S1, Section 1, for detailed information).

Assessments of physical function

At each time point, handgrip strength was measured using a grip strength dynamometer that was used in clinical practices at each institution. Two trials for each hand were performed, and the average of the highest results for each hand was calculated. Five-time-sit-to-stand test was performed at each time point. The patients were given verbal instruction according to the standardized protocol.¹⁷ The patients were allowed to practice the sit-stand transition once before performance of the timed trial. Each patient performed a single trial. At

Table 1 Assessments and interventions in the NEXTAC programme

Sessions ^a and time allocation	Assessments	Interventions
Nutritional session 30 min at T1 20 min at T2 and T3	<ul style="list-style-type: none"> • Food intake • Nutritional status (MNA) • Nutritional checklist^b • Skeletal muscle analysis • Diet diary collection (T2 and T3) 	<ul style="list-style-type: none"> • Nutritional advice • Support for NIS management, food environment, and eating-related distress • ONS prescription^c
Exercise session 30 min at T1 20 min at T2 and T3 for each programme	Assessment of physical function <ul style="list-style-type: none"> • 6 min walk distance (T1 and T3) • 5 m gait speed (T1 and T3) • Handgrip strength • Five-time-sit-to-stand test • Exercise diary collection (T2 and T3) Assessment of physical activity <ul style="list-style-type: none"> • Physical activity measurement • Physical activity interview 	Home-based resistance training <ul style="list-style-type: none"> • Prescription (T1) and modification (T2 and T3) of exercise programme • Instruction of exercise procedures • Education of self-modification Physical activity promotive counselling <ul style="list-style-type: none"> • Prescription (T1) and modification (T2 and T3) of target daily step • Physical activity counselling • Education of fall prevention

MNA, Mini Nutritional Assessment; NEXTAC, Nutrition and Exercise Treatment for Advanced Cancer; NIS, nutrition impact symptoms; ONS, oral nutritional supplement.

^aBaseline assessments were performed during the time between study entry and initiation of chemotherapy (T1 point). Subsequent assessments were at 4 ± 2 (T2 point) and 8 ± 2 (T3 point) weeks after the T1 point.

^bNutritional checklist to collect information about presence or absence of nutrition impact symptoms, problems in food environment, or eating-related distress.

^cA branched-chain amino-acids rich oral nutritional supplement (Inner Power®, Otsuka Pharmaceutical Co., Ltd., Japan) was provided one pack daily for 8 weeks.

T1 and T3 points, the 6 min walk test was conducted according to standard guidelines.¹⁸ A 30 m course was established in the corridor. Patients were monitored throughout the test using portable pulse oximetry. A single test was performed at each planned time point. The walking distance for 6 min was described as the 6 min walking distance. At T1 and T3 points, the 5 m gait speed was measured according to the standard protocol.¹⁹ The 10 m course was established in the corridor with a 5 m timing area in the middle. Patients were instructed to 'walk at a comfortable and normal pace' from end to end on the 10 m course. The time required to walk 5 m was measured using a manual stopwatch. The patient performed two tests with a short break between them. The shorter time of the two tests was used for analysis (see Supporting Information, Data S1, Section 2, for detailed information).

Assessments of physical activity

Physical activity (PA) was measured using an electronic pedometer/accelerometer with a storage capacity of 180 days (Kenz Lifecorder-GS, Suzuken Co., Ltd., Nagoya, Aichi, Japan).^{20,21} The device provided a record of the number of daily steps taken and the intensity of PA every 4 s throughout each day. When there was no digitized acceleration exceeded 0.06 g for 4 s, it was counted as non-device-wearing time. Collected data included the number of daily steps, the daily duration of device-wearing, and the daily duration of PA rated ≥ 1.8 or 3.9 metabolic equivalents (METs). Patients were instructed to wear the device for as long as possible in the daytime, starting from the time they changed clothes for

daily activity in the morning to the time they changed into nightclothes for sleep. Regular visits to the outpatient department of each institution allowed for data collection. Wearing the pedometer/accelerometer for ≥ 5 h in a day was defined as a device-wear day according to our preliminary observational study.²² Data on days with duration of device-wearing < 5 h a day were excluded from the analysis. After informed consent was obtained, the patients wore pedometers/accelerometers for > 7 days prior to study entry to measure baseline PA (pretreatment period). The average daily steps or the daily duration of PA during the pretreatment period was set as the individual's baseline value. The average daily steps or daily duration of PA between the T1 and T2 points was set as the individual's value for the T2 point. The average daily steps or daily duration of PA between the T2 and T3 points was set as the individual's value for the T3 point. Step count was visible on the device at any time. To promote self-feedback, we educated patients to check their step count for multiple times during the day. Every morning, they should record daily step count of the day before on diary (see Supporting Information, Data S1, Section 3.1, for detailed information).

Measurement of lumbar skeletal muscle mass index

Skeletal muscle mass at the third lumbar vertebra (L3) level was measured at points T1 and T3. The computed tomography images were obtained with or without contrast enhancement in 5 mm slice thicknesses. Two consecutive images extending from L3 to the iliac crest were chosen to measure

the cross-sectional area of the skeletal muscle that was identified based on Hounsfield unit thresholds of -29 to $+150$. The sum of the cross-sectional areas (cm^2) of the muscles in the L3 region was computed for each image. The mean value of two images was normalized for height in meters squared and reported as the lumbar skeletal muscle index (cm^2/m^2).²³ All analyses were performed using slice-O-matic software (version 5.0, Tomovision, Montreal, Quebec, Canada).

Diagnosis of muscle depletion and cancer cachexia

Muscle depletion was defined based on lumbar skeletal muscle index cut-offs of $<43.0 \text{ cm}^2/\text{m}^2$ for men with a BMI $<25.0 \text{ kg}/\text{m}^2$, $<53.0 \text{ cm}^2/\text{m}^2$ for men with a BMI $\geq 25.0 \text{ kg}/\text{m}^2$, and $<41.0 \text{ cm}^2/\text{m}^2$ for women.²⁴ Cancer cachexia was defined as unintentional weight loss of $>5\%$ during the preceding 6 months or $>2\%$ in patients with a BMI $<20 \text{ kg}/\text{m}^2$ or the presence of muscle depletion according to consensus criteria.¹²

Schedule of interventions

The NEXTAC programme was designed as a preventive intervention for disability, which could be carried out concurrently with the first-line systemic chemotherapy for the elderly patients with advanced cancer. The schedule and contents of interventions are summarized in Table 1. The NEXTAC comprised six sessions including three exercise and three nutritional sessions during an 8 week intervention period. Each component of the intervention was educational and promoted self-support. The first session for each intervention at the T1 point took ~ 30 min to present the programme to the patient. Follow-up interventions at the T2 or T3 points required ~ 20 min to review compliance and modify and optimize the programmes. Physicians recommended patients to attend each session with their caregivers or supporters to maximize the efficacy and safety of the interventions.

Nutritional intervention

Nutritional counselling was performed based on the standard protocol for cancer patients in the general population¹⁵ and the elderly population.²⁵ Individualized counselling aimed to educate patients on how to modify their usual meals by making them adhere to individual energy, protein, or other macronutrient requirements. The dietary advice had to specify the type and amount of food, the eating frequency, and calorie or protein amounts to achieve daily or dietary restrictions. The advice was further adjusted to personal eating patterns and preferences. They also provided information about non-pharmacological measures against NIS that were summarized in the instructor's manual. When pharmacological measures

for NIS were recommended, they sought cooperation with nurses and medical doctors. If patients had problems in their food environment or had eating-related distress and needed active psychosocial support, the information was shared with the nurses, medical doctors, psychotherapists, or/and medical social workers, and countermeasures were discussed. Oral nutritional supplements rich in branched-chain amino acids (Inner Power[®], Otsuka Pharmaceutical Co., Ltd., Japan) were provided for all patients in amounts of one pack daily for 8 weeks. One pack of Inner Power[®] (139 kcal/125 g) contains branched-chain amino acids (2500 mg), coenzyme Q10 (30 mg), and L-carnitine (50 mg).^{26,27}

Exercise intervention

Exercise interventions combined daily low-intensity resistance training with physical-activity counselling using an accelerometer.

Home-based resistance training

During each exercise session, the physiotherapist or occupational therapist assessed the patient's physical function and prescribed an individual exercise programme. The individualized exercise programme consisted of three to five of the following five exercise components: (i) sit-to-stand, (ii) calf raise, (iii) knee extension, (iv) knee raise, (v) side leg raise. Sit-to-stand was performed in three sets a day for 10 repetitions each set, and other exercises were also performed in three sets a day for 10 repetitions on each side. Three levels were prepared as follows:

Level 1: Programme consists of (i), (ii), and (iii).

Level 2: Programme consists of five exercises.

Level 3: Programme consists of five exercises and is done wearing 1-kg ankle-weights.

At the initial intervention T1 point, all patients performed Level 2 exercises under the supervision of the instructor. Then, home exercise was prescribed as follows:

- i. If the patient reported a modified Borg scale of 3 or 4 after completion of Level 2 exercise, the patient's home exercise prescription was determined to be at Level 2.
- ii. If the patient reported a modified Borg scale of ≤ 2 , the patient's home exercise prescription was determined to be at Level 3.
- iii. If the patient reported a modified Borg scale of ≥ 5 , the patient's home exercise prescription was determined to be at Level 1.

At the T2 or T3 point, the instructor assessed the patient's performance and tolerability of their home exercise regimen based on their exercise diary and direct interview. The

instructor then modified the exercise programme to the optimal level. Instructors educated patients not to discontinue exercise completely. They recommended modifying the programme in case of feeling too ill or tired to complete the full programme as prescribed. Self-modification included stepping down the next lower level in the programme or reducing the number of repetitions or sets. Patients were encouraged to return to the original level after their condition improved. Patients recorded their performance including the number of repetitions and sets and any use of ankle-weights in their exercise diary.

Physical activity promotive counselling

In each exercise session, the nurses, physiotherapists, or occupational therapists assessed the patient's PA and life style and prescribed individual target steps. The initial target step count was determined according to the average number of daily steps during the screening period as follows:

- i. If the patient's average steps were 2000 or less, the target step was 2000 steps. Instructors educated patients to go outside at least once a day.
- ii. If the patient's average daily steps were 2001 to 7999 steps, the target step was the average steps plus 2000 steps to a maximum of 8000 steps.
- iii. If a patient's average daily steps were ≥ 8000 steps, patients were educated to maintain their current level of PA.

At follow-up session in T2 or T3, instructors modified the target step according to the average steps taken during T1 to T2 or during T2 to T3 using the same prescription algorithm. During counselling, instructors explained the relationship between the patient's actual indoor or outdoor activity and the measured PA by showing them a summary report obtained from the analysis of the accelerometer software (Lifelyzer-05 coach, Suzuken, Japan). They discussed methods for increasing promotive factors and decreasing inhibitory factors of PA in the patient's actual daily living. If there was a need for active symptom control or social support to improve PA, the information was shared with the nurses, medical doctors, psychotherapists, or/and medical social workers, and countermeasures were discussed. Instructors explained the importance of fall prevention²⁸ for safety during PA as follows:

- i. When you feel dizziness or lightheaded, do not force yourself to walk more.
- ii. When you have pain in the knee or foot, numbness in the toe, or needs a walking stick/aid, pay careful attention to the possibility of fall.
- iii. Choose appropriate shoes that fit your foot. Do not use sandals or slippers when you walk.
- iv. Please review environmental hazards that could cause falls in your home, such as obstacles on the floor or difference in floor heights.

Statistical analysis

The primary endpoint of the study was feasibility defined as the proportion of patients attending ≥ 4 of six sessions, because we expected patients to receive feedback from each therapist at least once after the first intervention. We expected to reach 70% of attendance rate according to the attendance rate (70.8%) of randomized controlled trial of multimodal high intensity exercise intervention for patients with advanced cancer receiving chemotherapy.²⁹ We set the threshold value as 45% according to the completion rate (44%) of feasibility study for structured exercise programme for adult patients with advanced NSCLC who were receiving cancer treatment including chemotherapy.³⁰ The sample size was determined to be 30 based on the one arm exact binomial probability distribution with a statistical power ($1-\beta$) of 80% and two-sided significance level (α) of 10%.³¹ For the study to be considered sufficiently feasible to warrant further evaluation, the criteria were based on the attendance rate to achieve a lower confidence bound $\geq 45\%$. Compliance was assessed by the proportion of days the patients completed their diet or exercise diaries, consumed supplements, performed exercise, or wore pedometers/accelerometers ≥ 5 h a day during the intervention period. Each proportion was individually calculated as {performance day/intervention period} $\times 100$. Adherence was assessed by the proportion of patients who had adequate caloric or protein intake, kept or increased indoor or outdoor activity, increased total time spent in PA (≥ 1.8 METs), or achieved their target step. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The Wilcoxon signed-rank test was used for the pairwise comparison of measurement changes between study visits. *P* values < 0.05 were considered significant. All analyses were performed using JMP version 13.0 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patients

A total of 30 patients were enrolled to the study from 46 screened patients in four participating institutions during the 9 month registration period (Figure 1). Reasons for ineligibility included (i) patients chose the best supportive care without chemotherapy ($n = 5$); (ii) patients participated other clinical trials ($n = 5$); (iii) patients had no indication of chemotherapy at the time of enrolment ($n = 3$); (iv) patients declined participation to this study ($n = 2$); and (v) patients did not fulfil the stage criteria ($n = 1$). Twenty-four patients had NSCLC, and six patients had pancreatic cancer. The median age was 75 years (range, 70–84 years, Table 2). Three

patients had another cancer that needed no additional cancer treatment during the study period. Majority of patients were smokers, unemployed, and had no regular exercise habit; ~10% of patients were living alone and had recent history of falls. Cancer cachexia and muscle depletion were seen in 12 (40%) and 21 (70%) patients, respectively. All patients concurrently initiated chemotherapy and were included for assessments of attendance and safety. One patient withdrew their consent due to deteriorating health status from a respiratory infection unrelated to the study procedures. The remaining 29 patients were included for assessments of compliance, adherence, and efficacy.

Cancer treatment during the study period

All participants in this study started first-line chemotherapy within 4 days after the baseline assessment. The chemotherapy regimens for NSCLC patients included single-agent chemotherapy (docetaxel, vinorelbine, or pemetrexed) in 10 patients, platinum-based chemotherapy (cisplatin + pemetrexed or carboplatin + S-1) in four patients, epidermal growth factor receptor tyrosine kinase inhibitor (gefitinib or erlotinib) in eight patients with epidermal growth factor receptor gene mutations, and alectinib in two patients with a rearrangement of the anaplastic lymphoma kinase gene. Objective responses to cytotoxic regimens or targeted regimens against NSCLC were observed in 14.3% and 70.0% of patients, respectively. All patients with pancreatic cancer received gemcitabine + nab-paclitaxel. Objective responses in pancreatic cancer were 33.3%. None of our patients received immunotherapy, investigational treatments, or anti-cachexia medications such as megestrol acetate or eicosapentaenoic acid during the study period. Adverse events that were judged to be related to chemotherapy with

Table 2 Baseline patient characteristics

Variables	N = 30
Age, median (range)	75 (70–84)
Gender (women : men)	10:20
ECOG-PS, n (%)	
0	11 (36.7)
1	19 (63.3)
Cancer type, n (%)	
Non-small-cell lung cancer	24 (80.0)
Pancreatic cancer	6 (20.0)
Stage, n (%)	
III	3 (10.0)
IV or postoperative recurrence	27 (90.0)
Treatment, n (%)	
Cytotoxic regimen	20 (66.7)
Targeted regimen	10 (33.3)
Comorbidities, n (%)	
Chronic lung disease	13 (43.3)
Type 2 diabetes	9 (30.0)
Cardiovascular disease	7 (23.3)
Double cancer	3 (10.0)
Cerebrovascular disease	1 (3.3)
Lifestyle, n (%)	
Smoking history (yes)	21 (70.0)
Living alone	4 (13.3)
Unemployed	18 (60.0)
No exercise habit	16 (53.3)
History of falls in prior 1 month	3 (10.0)
Nutritional status	
Body mass index (mean ± SD)	21.7 ± 3.2
% weight change in prior 6 months	−3.0 ± 6.8
Cancer cachexia ^a	12 (40.0)
Skeletal muscle depletion ^b	21 (70.0)

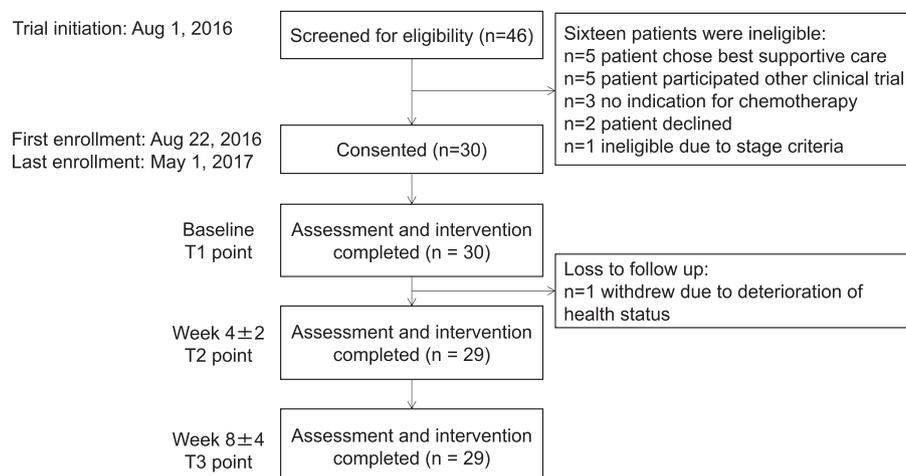
ECOG-PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

^aDiagnosis was based on the international consensus criteria.

^bSkeletal muscle depletion was defined as lumbar skeletal muscle mass index of <43.0 cm²/m² for men with a BMI <25.0 kg/m², <53.0 cm²/m² for men with a BMI ≥25.0, and <41.0 cm²/m² in women.

an incidence of >50% included anaemia (22 patients, 73%) and hypoalbuminemia (28 patients, 93%). Most of these adverse events were Grade 1 and were reversible.

Figure 1 Patient flowchart



Feasibility and attendance

Twenty-nine patients attended ≥ 4 of six planned sessions. The attendance rate was 96.7% (95% CI, 83.3 to 99.4) and met the primary endpoint. One man dropped out and missed four sessions at the T2 and T3 points. One woman accidentally missed one exercise session at the T3 point. She attended a make-up exercise session 9 days later, which exceeded the scheduled limit of the T3 point. The remaining 28 patients (93.3%) completed all sessions on time.

Compliance

The median intervention period was 57 days (Table 3). Patients completed diet and exercise diaries and consumed supplements during 90%, 94%, and 99% of their intervention period, respectively. The median proportion of days wherein patients performed full or self-modified exercise programmes was 91%. The median proportion of days wherein patients completed the prescribed exercise programme was 41% with a bimodal distribution peaking at 10% and 70%. Patients skipped or modified exercise programmes mainly due to feeling unmotivated or too ill. There was no specific predictor for poor exercise performance in baseline characteristics

including age, PS, gender, cancer type (pancreatic or lung), stage, types of chemotherapy, the presence of cachexia, or muscle depletion. Patients wore pedometers/accelerometers ≥ 5 h a day for a median of 98% of the total intervention days.

Adherence

Caloric and protein intakes were considered adequate by registered dietitians at 86% and 83% at the end of intervention, respectively. Indoor or outdoor activity was kept or increased in 79 and 69% of patients at the end of intervention, respectively. As a result, daily steps and time spent in PA (≥ 1.8 METs) increased in 66% and 59% of patients, respectively. The proportion of patients who achieved their target step was 24% at T2 point and 21% at T3 point.

Changes in physical parameters

All patients completed baseline assessments and follow-up assessments at T2 and T3 points were performed in 29 patients (Figure 1). The 6 min walk test at T3 point was cancelled in three patients by physiotherapists for safety reason including worsening of underlying arthritis in knee (in one patient) and deteriorating health status due to tumour progression

Table 3 Compliance and adherence

Period	Baseline to T2 point	T2 to T3 point	Baseline to T3 point
Number of patients	29	29	29
Intervention period (days)	29 (24–32)	28 (25–34)	57 (51–65)
Nutrition			
Diet diary fill-in day (%) ^a	96 (16–100)	95 (0–100)	90 (14–98)
Supplement consumption day (%) ^a	100 (96–100)	100 (80–100)	99 (88–100)
Adequate caloric intake, <i>n</i> (%) ^b	25 (89)	25 (86)	—
Adequate protein intake, <i>n</i> (%) ^b	24 (83)	24 (83)	—
Daily resistance training			
Exercise diary fill-in day (%) ^a	94 (67–100)	92 (22–100)	94 (51–98)
Performance day (%) ^c			
Full programme	56 (4–79)	17 (0–88)	41 (3–79)
Self-modified programme	29 (7–58)	42 (0–81)	42 (7–66)
Full or modified programme	89 (67–96)	90 (60–100)	91 (69–95)
Total performance day/intervention period for exercise (%) ^d			
Full programme	321/829 (39)	215/852 (25)	536/1681 (32)
Self-modified programme	262/829 (32)	297/852 (35)	559/1681 (33)
Full or modified programme	583/829 (70)	512/852 (60)	1095/1681 (65)
Physical activity			
Accelerometer wear day (≥ 5 h/day, %) ^a	100 (80–100)	100 (83–100)	98 (85–100)
Increased daily steps, <i>n</i> (%)	20 (69)	13 (45)	19 (66)
Increased time spent in PA (≥ 1.8 METs), <i>n</i> (%)	19 (66)	12 (41)	17 (59)
Maintenance or increase in indoor activity, <i>n</i> (%) ^e	25 (86)	23 (79)	—
Maintenance or increase in outdoor activity, <i>n</i> (%) ^e	20 (69)	20 (69)	—
Achievement of target step, <i>n</i> (%) ^f	7 (24)	6 (21)	—

METs, metabolic equivalents; PA, physical activity.

^aMedian (interquartile range) proportion of days in which patients filled in nutritional or exercise diaries, consumed supplements, or wore accelerometer ≥ 5 h a day during each term.

^bNumber (%) of patients whose caloric or protein intake during each term met their requirements assessed by registered dietitian.

^cMedian (interquartile range) proportion of days in which patients performed full, modified, or both of prescribed resistance training programme during each term.

^dCalculated as (total number of performance day/total intervention period) \times 100 for evaluable 29 patients.

^eNumber (%) of patients whose indoor or outdoor activity was maintained or increased from baseline during each term.

^fNumber (%) of patients whose mean daily steps during each term reached their individual target step.

(in one patient) or chemotherapy toxicity (in one patient). One patient (3.8%) had clinically significant decline (≥ 54 m) in 6 min walking distance.³ Body or skeletal muscle mass index, full Mini Nutritional Assessment score, caloric intake, 6 min walking distance, and gait speed were maintained during the study period (Table 4). Handgrip strength, five-time-sit-to-stand time, daily steps, and time spent in moderate-to-vigorous PA (≥ 3.9 METs) significantly improved at the T2 point. The five-time-sit-to-stand time and time spent in moderate-to-vigorous PA were improved through the T3 point.

Safety

Safety was assessed for all 30 patients. Adverse events possibly related to the NEXTAC programme were observed in five patients and included muscle pain (Grade 1 in two patients), arthralgia (Grade 1 in one patient), dyspnoea on exertion (Grade 1 in one patient), and plantar aponeurosis (Grade 1 in one patient). Four patients reported severe adverse events. One patient had Grade 4 hyponatremia due to cisplatin administration, two developed Grade 3 bacterial pneumonia, and one died of radiation pneumonitis. These were reviewed by the independent data and safety monitoring committee and were considered to be unrelated to the NEXTAC programme.

Discussion

The NEXTAC programme has three unique characteristics. First, this multimodal intervention was designed specifically for elderly cancer patients with high cachectic potential.

Second, it starts early after the diagnosis of advanced cancer and is performed concurrently with the first course of systemic chemotherapy. Finally, our exercise intervention combines daily low-intensity resistance training in the lower limbs and PA counselling.

In this feasibility study, we showed that the NEXTAC programme met a primary endpoint with sufficient patient attendance to sessions, an adequate safety profile, and few dropouts. Patients were compliant with consuming supplements, completing diaries, and wearing pedometers/accelerometers. Most of them were also adherent to meeting the recommended nutritional requirements, continuing home-based exercise, and keeping or increasing their indoor or outdoor activities.

It is challenging to maintain motivation and compliance with nutritional or exercise interventions in patients with advanced cancer.^{32,33} Baldwin *et al.*³⁴ reported detailed compliance data in their large randomized controlled study of nutritional intervention in patients with advanced malignancies and weight loss. The proportions of patients that completed food diaries and consumed supplements were 25% and 31% at baseline and 17% and 19% after 6 weeks intervention, respectively. They stopped the study early due to futility and suggested that poor compliance might limit efficacy.

Exercise interventions for advanced cancer have difficulty in recruitment, high attrition rate, and variable adherence.³⁵ Temel *et al.*³⁰ reported results of a feasibility study of moderate-intensity structured exercise for patients with advanced NSCLC. Twenty-four percent withdrew early without attending any sessions, and only 44% completed all planned sessions. The reasons for withdrawal or non-compliance included deterioration in health status, feeling unwell, concerns about the amount of travel, and hospitalizations.

Table 4 Changes in outcome measures

Parameters	Baseline value	No. of pairs (T2/T3) ^c	Changes from baseline to T2	Changes from baseline to T3
Physical constitution				
Body mass index (kg/m ²)	21.8 ± 0.6	29/29	-0.2 ± 0.2	-0.4 ± 0.2
Skeletal muscle index (cm ² /m ²)	40.7 ± 1.0	-/29	NA	-1.1 ± 0.5
Nutrition				
Full MNA score (point)	24.2 ± 0.8	29/29	0.2 ± 0.7	0.1 ± 0.9
Calorie intake (kcal/day)	1638 ± 65	29/29	74.3 ± 57.9	17.1 ± 65.7
Physical capacity				
6 min walking distance (m)	422.4 ± 12.8	-/26	NA	12.3 ± 10.9
5 m gait speed (m/s)	1.2 ± 0.04	-/28	NA	0.02 ± 0.04
Five-time-sit-to-stand test (s)	10.8 ± 0.4	29/28	-0.9 ± 0.5*	-0.5 ± 1.0*
Handgrip strength (kg) ^a	25.6 ± 1.2	28/28	1.7 ± 0.7*	0.2 ± 0.5
Physical activity				
Daily steps (steps/day)	4253 ± 463	29/29	571 ± 275*	417 ± 401
Time spent in PA (≥ 1.8 METs, min/day) ^b	47.1 ± 4.9	29/29	5.1 ± 2.9	3.8 ± 4.1
Time spent in MVPA (≥ 3.9 METs, min/day) ^b	5.0 ± 0.9	29/29	2.1 ± 0.8*	2.3 ± 1.1*

Data were presented as mean ± standard error. METs, metabolic equivalents; MNA, Mini Nutritional Assessment; MVPA, moderate or vigorous physical activity; NA, not assessed; PA, physical activity.

* $P < 0.05$ in Wilcoxon signed-rank test.

^aMean of maximum value in each side of hands.

^bSum of time rated for activity level of ≥ 1 or 4 in accelerometer (Lifecorder[®], Suzuken Co., Ltd.) corresponding to ≥ 1.8 or 3.9 METs.

^cNumber of pairs between baseline and T2 or T3 point.

Solheim TS. *et al.*¹³ recently reported results of their randomized phase II study of multimodal intervention in patients with advanced non-small-cell and pancreatic cancer. Their intervention consisted of nutritional counselling, exercise intervention, celecoxib, and supplements. The median age was 63 years, and 8% dropped out in the treatment arm. Compliance was 76% for celecoxib, 60% for exercise, and 48% for supplements. However, compliance for two or three combined was only 20–48% or 12%, respectively. This study showed the trade-off between number of interventions and level of compliance.

We tried to maximize compliance without reducing the efficacy of our intervention. We chose low-intensity exercise programmes as the exercise intervention. In community-dwelling elderly, low-intensity home-based resistance training with or without PA promotion is effective for increasing muscle mass, muscle strength, and gait speed³⁶ and preventing falls³⁷ with high compliance. Second, we tried to minimize patients' study participation burden by setting time limits for each session, carefully preparing to minimize appointment wait times, simplifying handouts and diaries, and reducing the number of assessments. Finally, we sought cooperation from patients' caregivers or supporters in attending sessions together as much as possible to maintain the patients' motivation and maximize intervention compliance. These modifications might contribute to the high compliance in the NEXTAC programme. However, we still have insufficient adherence because only 21% of patients achieved target steps, and compliant days in the full exercise programme were only 41% at the end of study period. Thus, we may need other measures such as regular phone calls or social networking services to keep patients motivated.

During the 8 week study period, skeletal muscle mass and physical function showed no significant deterioration in our patients. The 6 min walking distance was retained without clinically significant reduction except in one patient (3.8%). Previous reports suggest most patients lose their skeletal muscle^{1,2,7} and have clinically significant reductions in walking capacity in 29% of general age cases³ and 52% of the elderly population⁷ during chemotherapy for advanced NSCLC. Although this study was not designed to show the efficacy of the NEXTAC programme, our data might indicate the protective effect on skeletal muscle and physical function.

Our study has several limitations. First, our study population was heterogeneous in cancer type and treatment regimen. Second, we mainly assessed compliance and adherence via the patients' diaries, which potentially carried a risk of recall bias. Third, restrictive entry criteria in this study may limit the generalizability of the NEXTAC programme. Patients who needed assistance for activity of daily living at baseline (Barthel Index of ≤ 90) or had PS of 3–4 were excluded from the study cohort because they rarely had an indication for systemic chemotherapy. They needed a therapeutic or palliative intervention, which is outside the scope

of the preventive NEXTAC programme. Regarding patients with PS 2, we excluded them from the study cohort to assure the safety of unsupervised exercise programme at home. Elderly patients with PS 2 are vulnerable to adverse events during systemic chemotherapy including neutropenia, infection, or peripheral neuropathy especially in the platinum-based treatment,³⁸ which might increase the risk of falls.³⁹ Supporters who could monitor patients were also required in this study partially because of the same safety reason. In this study, there was no report of a fall, fracture, or other severe adverse event related to the home exercise programme. In addition, adverse events related to the systemic chemotherapy were not associated with decreased attendance, compliance, or adherence to the NEXTAC programme (data not shown). According to the satisfactory safety profile of the NEXTAC programme in this feasibility study, we expanded the eligibility criteria to PS 0–2 in the ongoing randomized phase two study (the NEXTAC-TWO study, Clinical Trial Registry No. UMIN000028801). Fourth, the impact of resistance training in lower limbs was not directly measured by the lower extremity strength test. We chose five-time-sit-to-stand test, walk speed, and 6 min walk test as outcome measures of our resistance training. Fifth, sample size of this study was too small to show the efficacy of the intervention. We should take careful attention to interpret the changes in physical parameters and await the results of ongoing NEXTAC-TWO study. Finally, our study included only Japanese patients. The medical environment varies among countries, and standards of care are rapidly changing. Thus, our results may not be directly transferable to different medical situations. However, reducing patients' burdens and improving compliance might be a crucial step in developing an effective multimodal intervention in any situation.

The combination of emerging anti-cachectic agents^{9,10} and non-pharmacological interventions will be the next step in this area. Our NEXTAC programme would be a good candidate for this combination, because it has no overlapping adverse events and might minimally reduce compliance of combination treatment. Based on the results of our study, we are currently conducting a prospective multicentre randomized phase II study of early exercise and nutritional interventions for elderly patients with advanced NSCLC and pancreatic cancer in Japan (the NEXTAC-TWO study). We hypothesize that early induction of NEXTAC might maintain physical function and prevent disability in elderly patients with advanced cancer who are at considerable risk of cancer cachexia.

Conclusions

Our multimodal intervention showed excellent feasibility and safety in elderly patients with newly diagnosed advanced

pancreatic and NSCLC receiving concurrent chemotherapy. Further randomized controlled studies are needed to determine the optimal combination of non-pharmacological treatments and their impact on the functional prognosis in this population.

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Supporting information

Conflicts of interest

The authors have declared no conflicts of interest.

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