Supportive Care in Cancer (2019) 27:1551–1561
https://doi.org/10.1007/s00520-018-4561-y

ORIGINAL ARTICLE

Undiagnosed cardiac deficits in non-small cell carcinoma patients in the candidate population for anti-cachexia clinical trials

Seyyed Mohammad Reza Kazemi-Bajestani[1] · Harald Becher[2] · Charles Butts[3] · Naveen S. Basappa[3] · Michael Smylie[3] · Anil Abraham Joy[3] · Randeep Sangha[3] · Andrea Gallivan[1] · Quincy Chu[3] · Vickie E. Baracos[1]

Received: 27 June 2018 / Accepted: 19 November 2018 / Published online: 13 December 2018

Abstract

Purpose Currently, there is no approved therapy for cancer cachexia. According to European and American regulatory agencies, physical function improvements would be approvable co-primary endpoints of new anti-cachexia medications. As physical functioning is in part dependent on cardiac functioning, we aimed to explore the cardiac status of a group of patients meeting current criteria for inclusion in cachexia clinical trials.

Methods Seventy treatment-naive patients with metastatic NSCLC [36 (51.4%) male; 96% ECOG 0–1; eligible for carboplatin-based therapy and meeting eligibility criteria for cachexia clinical trials] were recruited before the start of first-line carboplatin-based chemotherapy. Patients were evaluated by echocardiography, electrocardiography, and scales for fatigue and dyspnea. Computed tomography cross-sectional images were utilized for body composition analysis.

Results In 9/70 patients (12.8%), echocardiography allowed discovery of clinically relevant cardiac disorders [seven patients with left ventricular ejection fraction (LVEF) 32%–47%; one patient with severe right ventricular dilation and severe pulmonary hypertension and one patient with severe pericardial effusion warranted hospitalization and drainage]. Another 10/70 (14.3%) patients had diastolic dysfunction with preserved LVEF. The cardiac conditions were associated with aggravated fatigue ($p < 0.05$), dyspnea ($p < 0.05$), and anemia ($p = 0.06$). Five out of seven patients with LVEF < 50% were sarcopenic and one was borderline sarcopenic.

Conclusion Baseline cardiac status of the metastatic NSCLC patients adds potential heterogeneity for anti-cachexia clinical trials. Detailed cardiac screening data might be useful for inclusion/exclusion criteria, randomization, and post hoc analysis.

Keywords Cardiac status · NSCLC · Cachexia · Clinical trials

Introduction

Cancer cachexia contributes to poor prognosis, worsening of performance status, impaired quality of life, increased rate of chemotherapy toxicity, post-surgery complications (e.g., infection), and increased length of hospital stay [1]. Cachectic patients with non-small carcinoma (NSCLC) showed higher rate of unexpected hospital visits or hospitalizations, higher hospitalization-related medical expenses, and physical functional decline compared to non-cachectic patients [2, 3].

Cancer cachexia is an unmet clinical need; an approved therapeutic product does not currently exist. Several recent phase III clinical trials of cachexia therapy (Table 1) include the POWER trials, ROMANA trials, and MENAC trial. These trials focus on NSCLC and consider physical functioning as endpoints and interventions. In the POWER studies, a co-primary efficacy endpoint was physical function, tested by stair climb power [4]. In the ROMANA studies, a co- primary efficacy endpoint was handgrip strength [5]. The MENAC study (currently accruing patients) has several secondary functional endpoints including actigraphy, 6-min walk, and hand grip strength. Home-based self-assisted aerobic and resistance exercise program is the interventional exercise for MENAC

✉ Vickie E. Baracos
vickie.baracos@ualberta.ca

[1] Department of Oncology, Division of Palliative Care Medicine, University of Alberta, 11560 University Avenue, Edmonton, AB T6G 1Z2, Canada

[2] Department of Medicine, Division of Cardiology, Alberta Cardiovascular and Stroke Research Centre, Edmonton, Canada

[3] Department of Oncology, Division of Medical Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Canada

Table 1 Three recent randomized Phase III anti-cachexia clinical trials

	POWER	ROMANA	MENAC	Our study
Included patients	Stage III or IV NSCLC	Stage III or IV NSCLC	Stage III or IV NSCLC, pancreatic adenocarcinoma (stage III or IV) or inoperable cholangiocarcinoma	Stage IV NSCLC
Age (year)	•Men: aged ≥ 30 years •Women: aged ≥ 30 years with clinical confirmation of postmenopausal status	> 18	18–80	> 18
Standard therapy	First line platinum plus a taxane (POWER 1) or platinum plus a non-taxane agent (POWER 2)	Any chemotherapy and/or radiotherapy	Any chemotherapy and/or radiotherapy	First line carboplatin-based chemotherapy
Trial identifier	NCT01355484 NCT01355497	NCT01387269 NCT01387282	NCT02330926	–
N	*N* = 600	*N* = 979	*N* = ongoing	*N* = 50
Intervention	Enobosarm® nonsteroidal selective androgen receptor modulator	Anamorelin® growth hormone secretagogue receptor type 1 (ghrelin receptor) agonist	multimodal intervention (resistance & aerobic exercise, nutrition and ibuprofen)	None
Excluded BMI	BMI > 32 kg/m^2	BMI > 30 kg/m^2	BMI > 30 kg/m^2	None, 16 (22.9%) > 30 kg/m^2; 10 (14.3%) > 32 kg/m^2
Inclusion cachexia criteria	None specified	Involuntary weight loss of ≥ 5% body weight within 6 months at baseline or BMI < 20 kg/m^2	None specified	None specified
Time of intervention	Before start of first-line chemotherapy	Before or after chemotherapy and/or radiation therapy	Before first- or second-line anticancer therapy	Before start of first-line chemotherapy
Performance status	ECOG ≤ 1	ECOG ≤ 2	Karnofsky score > 70	ECOG ≤ 2; 95.7% ECOG 0–1 enrolled
Cardiovascular considerations (exclusion criteria)	Clinically concurrent illness that would interfere with protocol (investigator judgment); Uncontrolled hypertension, congestive heart failure, or angina; Baseline stair climb time ≥ 30 s (mean of two stair climb tests).	Uncontrolled diabetes mellitus; Other clinical diagnosis, ongoing or inter-current illness that in the investigator's opinion would prevent the patient's participation	Positive history of heart disease, i.e., severe (NYHA class III or IV) congestive heart failure, uncontrolled hypertension, history of previous myocardial infarction, unstable angina, coronary revascularization, uncontrolled arrhythmia, and cerebrovascular accident	Dilated, hypertrophic, or diabetic cardiomyopathy; recent acute coronary syndrome, stroke, PVD requiring intervention; uncontrolled diabetes or hypertension

ECOG Eastern Cooperative Oncology Group, *NYHA* New York Heart Association, *MENAC* Multimodal Intervention for Cachexia in Advanced Cancer Patients Undergoing Chemotherapy, *POWER* Clinical Development Program of Enobosarm, a Selective Androgen Receptor Modulator, for the Prevention and Treatment of Muscle Wasting in Cancer Patient, *PVD* peripheral vascular disease, *ROMANA* Anamorelin in patients with non-small-cell lung cancer and cachexia

study. There has been little agreement on approaches/endpoints in anti-cachexia clinical trials [6]. The clinical benefits of proposed therapies for cancer cachexia are controversial [6]. According to the European and American regulatory agencies, one of the major expected clinical benefits is described as improvement of physical function tests (stair climbing test, handgrip as co-primary endpoint) [6, 7]. In the MENAC study, exercise is both an intervention and an endpoint. Although physical function improvement is in clear focus as an endpoint reflecting clinical benefit to the patient, one of the major sources of physical function fluctuations (cardiac function) has not been thoroughly considered. Most cachexia clinical trials include patients who are candidates for standard chemotherapy, and therefore have acceptable performance status [usually Eastern Cooperative Oncology Group (ECOG) score 0–1]. Specific indicators of intact cardiovascular function are not part of cachexia trial inclusion criteria; however, patients with a prior history of severe heart failure are excluded (Table 1). Considering locally advanced or metastatic non-small cell carcinoma (NSCLC), a patient population which is currently a focus for cachexia clinical trials, ischemic heart disease, cardiac dysrhythmia, and heart failure is relatively common comorbidities [8]. Therefore, the presence of overt and non-overt cardiac disorders in NSCLC patients is to be expected. We hypothesized that cardiac screening of metastatic NSCLC patients who are potentially eligible candidates for cachexia clinical trials might reveal cardiac abnormalities.

Material and methods

Patient population/eligibility and exclusion criteria

This study was approved by the Health Research Ethics Board of Alberta. From October 2013 till May 2016, 91 patients were referred by medical oncologists and were approached for consent form (Fig. 1). Patients had metastatic NSCLC and were eligible for first-line carboplatin-based therapy. In addition to the general eligibility of carboplatin-based therapy (ECOG ≤ 2), we excluded the patients who had any other active malignancy, except for adequately treated carcinoma in situ, basal cell carcinoma and squamous cell carcinoma of the skin, as well as curative malignancy with no recurrence for more than 5 years. Consistent with exclusion criteria of cachexia clinical trials, patients with known dilated, hypertrophic, or diabetic cardiomyopathy, within 3 months having acute coronary syndrome [including unstable angina or myocardial infarction (MI)], ischemic or hemorrhagic cerebrovascular disease, or peripheral vascular disease requiring revascularization, or coronary artery bypass graft or percutaneous coronary angioplasty and baseline blood pressure > 180/110 mmHg were excluded. Patients with either *uncontrolled* hypertension or *uncontrolled* diabetes mellitus were not included. Full cardiac evaluation [echocardiography and electrocardiography (ECG)] were performed for 70 patients (Fig. 1 and Table 2). Previous history of weight loss at baseline (> 5% in recent 6 months) or low BMI was not a requirement for inclusion in our cohort, in concordance with recent clinical trials (Table 1). These features are not considered mandatory at baseline, as cancer cachexia clinical trials are conducted in tumor groups with a uniformly high risk of weight loss both before and after diagnosis, including NSCLC.

Electrocardiography and echocardiography

Echocardiography was performed using an Epiq® scanner (Philips Medical systems, Bothell, WA, USA) according the 2015 ASE/EACVI Recommendations for Chamber Quantification and 2016 Recommendations for Evaluation of Diastolic Function by Echocardiography [9]. LVEF was calculated using the biplane Simpson method. Global longitudinal strain (GLS) measurements were made in the three standard apical views. Average GLS from the three views was reported. LV diastolic function was graded normal, mild (grade 1), moderate (grade 2), and severe (grade 3) depending on the measurements of pulsed wave Doppler of mitral inflow, tissue Doppler of mitral annulus movement, left atrium volume measurement, and CW-Doppler of the tricuspid regurgitation if present [9].

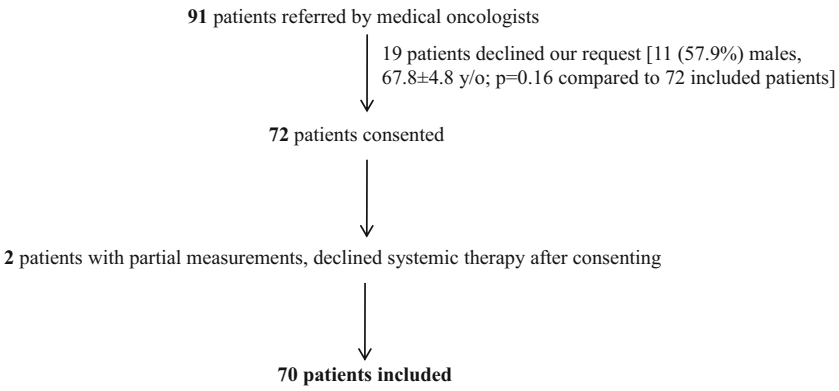

Fig. 1 Patient inclusion

Table 2 Patients' characteristics, 70 metastatic NSCLC patient candidates for carboplatin-based palliative therapy

Demographic data	Age (year)	65.7 ± 8.5
	Caucasian *n* (%)	68 (97.1)
Tumor histology	Adenocarcinoma	48 (68.6)
	Squamous cell carcinoma	17 (24.3)
	Others	5 (7.1)
Cardiovascular risk factors/background	Hypertension n (%)	28 (40.0)
	Diabetes mellitus *n* (%)	10 (14.3)
	Smoking *n* (%)	56 (80)
	Myocardial infarction *n* (%)	6 (8.6)
Biochemical parameters	White blood cell ($\times 10^9$/L)	9.2 ± 4.4
	Hemoglobin (g/L)	129.7 ± 15.4
	Anemia[a]	32 (45.7)
	Platelet (g/L)	341.1 ± 117.4
	Creatinine (μmol/L)	75.2 ± 25.9
	Na (mmol/L)	139.9 ± 3.2
	K (mmol/L)	4.6 ± 0.48
	Aspartate aminotransferase (U/L)	29.6 ± 18.1
	C-reactive protein > 10 (mg/L)	37 (52.9)
Drug history within 1 month before start of chemotherapy	Angiotensin-converting-enzyme inhibitor *n* (%)	11 (15.7)
	Angiotensin receptor blocker *n* (%)	9 (12.8)
	Beta-blocker *n* (%)	14 (20)
	Statins *n* (%)	15 (21.4)
Performance/functional status	ECOG (0–1)	67 (95.7)
	MRC (1–2)	61 (87.1)
	FACIT-F	33.0 ± 11.9
Echocardiography findings	Left ventricular ejection fraction (%)	58.5 ± 7.5
	Left ventricular ejection fraction < 50% *n* (%)	7 (10)
	Global longitudinal strain (%)	18.4 ± 3.1
	Global longitudinal strain < 18% *n* (%)	25 (35.7)
	Left ventricular mass/body surface area (g/m^2)	86.4 ± 22.9
	Abnormal diastolic dysfunction[b]	18 (25.7)
	Pericardial effusion	18 (25.7)
Electro-cardiography findings	Rate (beats/min)	78.7 ± 15.2
	QRSD > 120 ms *n* (%)	7 (10)
	Abnormal QTc[c] *n* (%)	28 (40)
	PR > 200 ms *n* (%)	9 (12.9)
Anthropometric/body composition	History of > 5% weight loss	34 (48.6%)
	Body mass index (kg/m^2)	26.3 ± 5.6
	BMI < 20 kg/m^2	4 (5.7)
	Body mass index > 32 kg/m^2	10 (14.3)
	CT-defined skeletal muscle area/height^2 (cm^2/m^2)	46.2 ± 10.9
	CT-defined muscle attenuation (HU)	29.3 ± 9.0
	CT-defined total adipose tissue area/height^2 (cm^2/m^2)	104.6 ± 63.5
	Sarcopenia *n* (%)	38 (54.2)

CT computed tomography, *ECOG* Eastern Cooperative Oncology Group, *FACIT-F* The Functional Assessment of Chronic Illness Therapy-Fatigue scale [score], *MRC* medical research council

[a] Anemia defined as hemoglobin < 135 g/L for males and < 120 g/L for females before start of chemotherapy

[b] Grade 1, 2, or 3

[c] QTc > 440 ms in men or > 460 ms in women

Routine 12 lead ECG was performed and major parameters including heart rate, PR, QRS duration (QRSD), and QT corrected (QTc) were abstracted.

Performance status, shortness of breath, and fatigue

Performance status was assessed by using ECOG [10]. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale was used for assessment of fatigue [11]. Medical Research Council (MRC) Breathlessness Scale [12] was applied for evaluation of dyspnea.

Clinical assessment of patients

Past medical history and drug history (within 1 month before referral to our study) were abstracted through medical charts.

Body composition analysis

Baseline computed tomography (CT) cross-sectional images at the third lumbar vertebrae were used to assess body composition. This method has been validated in several previous publications in cancer patients [1].

Statistical analysis

We used SPSS software version 24 (Chicago, IL, USA) for data analysis. Kolomogorov-Smirnov test was considered to assess the normality of the variables. *t* test and Chi-square tests were applied for comparison of quantitative and categorical variables, respectively. A $p < 0.05$ was considered statistically significant. Overall survival was defined as the number of days from the first day of carboplatin-based therapy until death. Patients were monitored until the actual date of death or March 1st 2017.

Results

Overall features of the population

Demographic, biochemical, medical, and cachexia-related features are shown in Table 2. The mean age of our patients was 65.1 ± 8.0 years old [$N = 70$, 36 (51.4%) males, 68 (97.1%) were Caucasian; 67/70 (95.7%) were within ECOG 0–1]. The mean FACIT-F fatigue score was 33.0 ± 11.9 for all the patients [score 52 is the highest (i.e., normal) score]. Twenty-eight/70 patients (40.0%) had a history of hypertension and 17 (24.3%) were diabetic. Eighty percent of our patients were smokers and 6/70 (8.6%) patients had a history of MI event (remote, not within 3 months of referral. Body mass index (BMI) was 26.3 ± 5.6 kg/m^2; sarcopenia (i.e., skeletal muscle depletion based on previously described cut-offs) [13] was found in 54% of patients.

Echocardiography and ECG findings

The average of echocardiography-defined LVEF was 56.7% ± 7.5%. Overall, seven (10%) of our patients had LVEF < 50% (32–47%). Twenty-five patients (35.7%) had abnormal GLS (i.e., less than 18%) (Table 2). ECG-defined QRSD and QTc abnormalities were found in 10% and 40% of patients, respectively; 25.7% of patients had abnormal diastolic dysfunction (Table 2).

Abnormal cardiac findings

Based on the cardiac evaluations, we categorized patients into three groups (Table 3): (1) *critical cardiac findings*: patients with classic finding of systolic heart failure (LVEF < 50%) or any cardiac finding that warrants admission or major interventions; (2) patients with any degree of diastolic dysfunction [9] with preserved LVEF (> 50%) (*DDPEF*); and (3) patients with no major cardiac finding.

Critical cardiac findings are presented in Table 4. Clinically relevant cardiac disorders were discovered in 9/70 (12.9%) patients (and were previously unknown in 8 out of 9 patients) (Table 3). Patient #53 was the only one with a recent cardiac history (ischemic cardiomyopathy/heart failure in recent year). None of the other patients in this group had a current medical history of heart failure. Severe cardiac dysfunction of patient study# 17 resulted in treatment plan cancelation and initiation of maintenance therapy. However, the treating oncologist initiated the treatment plan in all other patients. Seven patients in this group had classic findings of systolic dysfunction likely due to pre-existing ischemic pathology (all had regional wall motion abnormality-wall motion index > 1). Two other critical findings were reported. Patient #66 was discovered to have massive pericardial effusion at echocardiography and was very close to having cardiac tamponade. Patient was admitted immediately after echocardiography and pericardiocentesis took place and patient discharged symptom-free. For patient #29, severe right ventricular dilatation and severe pulmonary artery hypertension were discovered in echocardiography.

Ten (14.3%) patients found to have different degrees of DDPEF. One of these had a history of MI 16 years previously (#43) and another had an echocardiography-defined evidence of DDPEF 2 years previously. Characteristics of patients with DDPEF are shown in Table 5. Among patients with DDPEF, three had sarcopenic obesity (patients #4, #13, #73) (Table 4). Patients with DDPEF found to be more fatigued compared to patients without major cardiac findings ($p < 0.01$) (Table 3).

Even though our patients had passed the cardiac-related exclusions for receiving carboplatin-based chemotherapy as well as additional cardiac-related exclusions (Table 1), our study assessments revealed numerous cardiac abnormalities which had not previously been diagnosed. No comorbidities consistently associated with the presence of cardiac

Table 3 Subgroups based on cardiac findings

	No major cardiac finding ($n = 51$)	Critical cardiac findings ($n = 9$)	Diastolic dysfunction with preserved ejection fraction (DDPEF) ($n = 10$)	All patients with abnormal cardiac findings (critical findings or DDPEF ($n = 19$)[a]
Age (year)	64.1 ± 7.9	68.3 ± 8.6 ^{NS}	67.3 ± 7.1 ^{NS}	67.7 ± 7.6^{NS}
Male *n* (%)	24 (47.1)	7 (77.8) ^{NS}	6 (60.0) ^{NS}	13 (68.4) ^{NS}
ECOG (0–1) *n* (%)	58 (95.1)	9 (100) ^{NS}	10 (100) ^{NS}	19 (100) ^{NS}
Dyspnea-MRC score	1.7 ± 0.5	2.4 ± 0.5**	1.8 ± 0.6 ^{NS}	2.1 ± 0.6*
Fatigue-FACIT	34.8 ± 11.6	30.2 ± 12.6	26.1 ± 10.4*	28.0 ± 11.4*
Sarcopenia *n* (%)	28 (54.9)	6 (66.7)^{NS}	4 (40) ^{NS}	10 (52.6)^{NS}
History of > 5% weight loss *n* (%)	23 (45.1)	4 (44.4) ^{NS}	7 (70) ^{NS}	34 (48.6) ^{NS}
Body mass index (kg/m^2)	26.2 ± 5.8	24.9 ± 3.6 ^{NS}	27.6 ± 6.1 ^{NS}	26.42.1 ± 5.1 ^{NS}
BMI < 20 kg/m^2	3 (5.8)	0 (0) ^{NS}	1 (10) ^{NS}	1 (5.2) ^{NS}
CRP > 10 mg/L	24 (47.1)	6 (66.7) ^{NS}	7 (70) ^{NS}	13 (68.4) ^{NS}
History of > 5% weight loss AND CRP > 10 kg/m^2	12 (23.5)	4 (44.4) ^{NS}	6 (60) ^{NS}	10 (52.6)*
BMI > 32 kg/m^2	9 (17.6)	0 (0) ^{NS}	1(10) ^{NS}	1 (5.2) ^{NS}
Anemia	19 (37.2)	6 (66.7)^{NS}	7 (70)$^{\#}$	13 (68.4) ^{NS}
Hypertension *n* (%)	19 (37.2)	4 (44.4) ^{NS}	5 (50) ^{NS}	9 (47.4) ^{NS}
Diabetes mellitus *n* (%)	7 (13.7)	2 (22.2) ^{NS}	1 (10) ^{NS}	3 (15.8) ^{NS}
Median overall survival (days)	221	159 ^{NS}	238 ^{NS}	207 ^{NS}

In the patients with critical cardiovascular findings (Table 2), among the first seven patients with impaired LVEF and symptoms of classic heart failure, five patients were sarcopenic, and one patients was borderline sarcopenic (SMI = 54 cm^2 /m^2 , *z* score = 0.2). Only one patient had non-depleted skeletal muscle index

ECOG Eastern Cooperative Oncology Group, *FACIT-F* The Functional Assessment of Chronic Illness Therapy-Fatigue scale [score], *MRC* medical research council

[a] Values in this column are compared to the column related to patients with non major cardiac findings

#$p = 0.06$, *$p < 0.05$, **$p < 0.01$

abnormalities. Regarding obesity, no patients with critical cardiac finding and only one patient within DDPEF had BMI > 32 kg/m^2. Patients with cardiac abnormalities were also not more likely to have a history of diabetes mellitus or hypertension, than those without cardiac abnormalities (Table 3).

Some manifestations of cachexia and symptoms associated with the presence of cardiac abnormalities. Baseline CRP > 10 mg/L or sarcopenia at baseline were not significantly associated with cardiac abnormalities. However, patients with concurrent history of > 5% weight loss and increased CRP were more likely to display cardiac abnormalities (Table 3). Patients with critical cardiac findings had more dyspnea ($p < 0.01$) and patients with DDPEF had more fatigue ($p < 0.05$) compared to patients without major cardiac findings (Table 3). Also, anemia was more prevalent in patients with cardiac abnormalities (Table 3).

Discussion

We focused our analysis on sample of NSLC patients in first-line therapy who conformed to criteria of eligibility for recent randomized phase III clinical trials of cancer cachexia therapy. A detailed evaluation of the cardiac function of this clinical trial–eligible population reveals a disturbingly heterogeneous cardiac profile and symptom burden (fatigue, dyspnea, anemia, sarcopenia) that would plausibly have significant impact on the ability of these patients to perform physical functions as trial endpoints or interventions. The presence of heart failure or impaired diastolic function was often concurrent with severe dyspnea, fatigue, sarcopenia, and/or anemia, all of which are individually associated with functional limitation.

Our patients conformed to the cardiovascular inclusion/exclusion criteria of cachexia clinical trials (Table 1). When these criteria are applied to our NSCLC population, individuals with critical cardiac findings, as well as those with DDPEF would be eligible to be participants in the clinical trials. Only 1/70 patients (1.4%) had a known current diagnosis of heart failure based on medical history (Table 1); however, echocardiographic examination revealed a 13% rate of heart failure/critical cardiac conditions and 14.3% of the sample had DDPEF. Several major phase III clinical trials focused on NSCLC patients due to high prevalence and progressive nature of cachexia in this group of patients. In three major regulatory agency-authorized clinical trials (Table 1), a cardiac history was taken but cardiac assessment was not included (Table 1). The cardiac-related inclusion and exclusion criteria

Table 4 Characteristics of patients with critical cardiovascular findings

Study #, gender, age, *BMI*	Risk factors	Drug history	LVEF (%)	GLS (%)	Diastolic dysfunction	ECG	Known cardiac disease	Known CHF in recent year	Overall survival (days)	Others
09, F, 56, *23*	Dyslipidemia, smoking	Statins	40.9	13.0	Grade I	Sinus tachy-cardia	No	No	109	Sarcopenic; FACIT-F = 41; MRC = 2
10, M, 61, *30.1*	Hypertension, diabetes mellitus type II, smoking	Beta-blocker, spironolactone	42.0	7.0	Grade II	Atrial fibrillation	??	No	159	FACIT-F = 10; MRC = 3
12, M, 79, *31.1*	Diabetes mellitus type II, smoking	Beta-blocker, angiotensin-converting-enzyme inhibitor	47.0	15.6	Grade I	Right bundle branch block	Myocardial infarction	No	153	Borderline sarcopenic (SMI = 54, zscore = 0.2); FACIT-F = 21; MRC = 3
17, M, 67, *22.9*	Smoking	No	32.2	11.6	Grade I	Interventricular conduction delay	No	No	156	Main treatment plan canceled Sarcopenic; FACIT-F = 31; MRC = 2
53,M,68, *20.3*	Smoking	Beta-blocker, statins	35.4	15.2	Grade I	Ischemic pattern	Myocardial infarction, ICM	Yes	> 365	Sarcopenic; FACIT-F = 44; MRC = 2
71, M, 84, *24.6*	Hypertension, smoking	Beta-blocker, ACEI, statins	44.4	17.5	Grade I	Right bundle branch block	Myocardial infarction	No	253	Sarcopenic; FACIT-F = 44; MRC = 2
38, F, 64, *24.4*	Dyslipidemia, smoking	Statins	46.7	18.8	Grade I	Normal	No	No	> 365	Sarcopenic; FACIT-F = 33; MRC = 2
66, M, 69, *25.7*	hypertension, Dyslipidemia, smoking	Angiotensin-converting-enzyme inhibitor, statins	52.1	N/A[a]	Grade I	Normal	CAD	No	207	Pericardial effusion, admitted for drainage; FACIT-F = 14; MRC = 3
29, M, 67, *23.6*	Hypertension, smoking	Angiotensin receptor blockers	55	18.1	Negative	Ischemic pattern	No	No	97	Severe PHTN; severe RVD; sarcopenic; FACIT-F = 34; MRC = 3

CAD coronary artery disease, *FACIT-F* The Functional Assessment of Chronic Illness Therapy-Fatigue scale [score], *ICM* ischemic cardiomyopathy, *MI* myocardial infarction, *MRC* medical research council shortness of breath scale [score], *PHTN* pulmonary hypertension, *RVD* right ventricular dilation

[a] Not available due to technical issues (poor window)

Table 5 Characteristics of ten patients showed diastolic dysfunction with preserved ejection fraction

Study #, gender, age, *BMI*	Risk factors	Drug history	LVEF (%)	GLS (%)	Diastolic dysfunction	ECG finding	Known cardiac disease	Overall survival (days)	Others
04, F,70, *31.4*	No	No	59	22	Grade II	Ischemic pattern	No	> 365	Sarcopenic; FACIT-F = 48; MRC = 1
5, M,71, *23.1*	Dyslipidemia, smoking	No	61	17	Grade II	Normal	No	51	FACIT-F = 13; MRC = 2
11, F, 73, *20.0*	No	Beta-blocker, statins	53	18	Grade I	Ischemic pattern	Myocardial infarction	290	FACIT-F = 30; MRC = 2
13, M, 56, *39.8*	Dyslipidemia, hypertension, smoking	Beta-blocker, ACEI, statins	60.3	16.9	Grade I	Left atrial abnormality	Myocardial infarction	226	FACIT-F = 28; MRC = 3
24, F, 64, *27.5*	Dyslipidemia, hypertension, smoking	Beta-blocker, statins	58.8	21.5	Grade II	Atrial premature complexes	No	> 365	FACIT-F = 29; MRC = 2
43,M,65, *24.6*	Smoking	Statin, ARB	52.4	15.4	Grade I	Normal	Myocardial infarction	251	FACIT-F = 14; MRC = 2
49, M, 71, *29.8*	hypertension, smoking	ARB	54.4	18.30	Grade I	RBBB	DDPEF	43	Sarcopenic; FACIT-F = 32; MRC = 2
51,M,55, *19.9*	Smoking	No	51	15.8	Grade I	Normal	No	141	Sarcopenic; FACIT-F = 19; MRC = 2
58, M, 75, *28.1*	Dyslipidemia, hypertension	Beta-blocker, ACEI, statins	59	??	Grade I	Ischemic pattern	No	175	MRC = 1
61, F, 73, *32.1*	Dyslipidemia, hypertension, diabetes mellitus, smoking	ACEI, statins	63	20	Grade II	Normal	No	266	Sarcopenic; MRC = 1

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blockers, *DDPEF* diastolic dysfunction with preserved ejection fraction, *FACIT-F* The Functional Assessment of Chronic Illness Therapy-Fatigue scale [score], *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *RBBB* right bundle branch block, *MRC* medical research council shortness of breath scale [score]

typical of recent trials were not specific enough to have been able to identify the kinds of patients we saw with notable cardiac impairment (i.e., exclusion in the POWER studies of "concurrent illness based on investigator judgement" or exclusion in the MENAC study of "NYHA class III or IV cardiac dysfunction") (Table 1). On the other hand, a general exclusion of "[any] history of MI or cardiac intervention" (MENAC) (Table 1) may exclude several patients for whom these events were far in the past, and without a clear implication for trial participation. As we saw in our study, four out of six patients with a prior history of myocardial infarction were within the normal cardiac function group.

It was not our intention to conduct functional measures such as stair climbing test or hand grip on our patients, but we speculate that their cardiac function would influence their ability to perform functional tests of different types. Classic heart failure [14] as well as DDPEF [15] both associate with depletion of skeletal muscle mass and strength and also functional parameters such as 6-min walk test. In cardiology, heart failure is defined as an insufficient heart to response to demands of the tissue (mainly skeletal muscle), which contributes to fatigue and dyspnea. Accordingly, reduced capacity for aerobic exercise is the hall mark of heart failure [16]. Therefore, we speculate that cardiac disorders may pose a limitation to the physical functioning in NSCLC patients at risk for cachexia.

Exercise performance capacity as evaluated by peak oxygen consumption (peak VO_2) was reduced in colorectal cancer patients with skeletal muscle depletion compared to control subjects and this maladaptation of the heart was independent of chemotherapy [17]. Furthermore, some of the cancers such as lung cancer share similar risk factors with atherosclerotic cardiovascular diseases, i.e., aging, smoking, and hyper-inflammatory status. Existence of prolonged chronic obstructive pulmonary diseases in lung cancer patients could generate backward pressure on the right side of the heart. Possibly, the heart also can be functionally and structurally damaged in patients with cancer as cardiac muscle appears vulnerable to the same catabolic cascades as skeletal muscle and adipose tissue [8, 18].

Our findings may be important for trials in advanced NSCLC patients for the indication of cachexia, and fatigue, as well as investigations in which exercise is the intervention (e.g., NCT01581346, NCT01136083). Cancer fatigue is a multifactorial syndrome that thought to encompass several etiologies including inflammation, anemia, treatment side effects, psychologic burden, and muscle loss [19]. New therapies for cancer fatigue are under investigation (e.g., NCT00866970, NCT00040885, NCT00829322) [20]. Both fatigue and cancer cachexia are outcomes of similar pathophysiologic pathways, mainly activated immune response as a consequence of tumor presence [21]. Patients with advanced NSCLC suffer from progressive aggravation of symptoms such as fatigue and dyspnea, and these are among the most prevalent symptoms in this group of vulnerable patients [22, 23]. Dyspnea in lung cancer patients might be a consequence of tumor, treatments, comorbidities such as chronic obstructive pulmonary disease, cardiovascular diseases, or progressive cachexia [24]. Anemia is a prevalent finding in both cancer and heart failure settings; in our study, anemia was prevalent in patients with cardiac abnormalities; anemia prevalence is high in either systolic or diastolic heart failure and is associated with reduced hand grip [25].

Our findings suggest an additional level of complexity to be considered in patient populations at risk for cachexia. Physical functioning in various forms is proposed both an intervention and an endpoint in cachexia investigations, and it would seem prudent to evaluate each patient's cardiac function, as relevant to the specific exercise interventions and endpoints. Echocardiography may be the most convenient and cost-effective way to make the determination of cardiac function. We did not otherwise identify any comorbidities or clinical predictors that would robustly identify the patients with heart failure in our sample.

We presented a discussion of the possible concurrent evolution of cancer cachexia and heart failure in our 2014 review [8] and discussed how these conditions may mutually exacerbate one another. Classic heart failure is associated with weight loss and skeletal muscle (i.e., cardiac [-induced] cachexia) [8, 14]. Cancer cachexia effects on the human heart have not yet been the subject of prospectively conducted investigations; however, in experimental animals with cancer cachexia, there is progressive cardiac atrophy, associated with reduction in LVEF [8]. While we may diagnose patients with cachexia and work to develop treatments for the indication of cancer cachexia, we would do well to always keep in mind the polymorbid character of patients with NSCLC.

Limitations

Our characterization of cachexia was mainly focused on CRP, weight loss history, and presence of sarcopenia, and we did not collect information on serum albumin, anorexia, or food intake. Albumin is not standard blood work for all of our patients and CRP is more widely accepted as a cachexia biomarker. We recognize the deficit in anorexia/food intake. The significance of findings such as decreased GLS, increased QRSD, abnormal QTc, and prolonged PR in 36%, 10%, 40%, and 13% of patients, respectively, remain unclear. The impact of these findings on further functional measurements needs further investigations.

Conclusion

Comprehensive measurements of cardiac status and related symptoms (dyspnea and fatigue) will underpin a more useful anti-cachexia clinical trial design.

Funding information SMRKB received scholarship support from Alberta Innovates Health Solutions, the Queen Elizabeth II Graduate Scholarship, Izaak Walton Killam Memorial Foundation and Dr. Herbert Meltzer Family. VEB is supported by the Canadian Institutes of Health Research and the Alberta Cancer Foundation.

Compliance with ethical standards

This study was approved by the Health Research Ethics Board of Alberta.

Conflict of interest The authors declare that they have no conflict of interest. First author and corresponding author of this work have full control of all primary data and agree to allow the journal to review their data if requested.

References

1. Kazemi-Bajestani SM, Mazurak VC, Baracos V (2015) Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Semin Cell Dev Biol 54:2–10. https://doi.org/10.1016/j.semcdb.2015.09.001
2. Naito T, Okayama T, Aoyama T, Ohashi T, Masuda Y, Kimura M, Shiozaki H, Murakami H, Kenmotsu H, Taira T, Ono A, Wakuda K, Imai H, Oyakawa T, Ishii T, Omori S, Nakashima K, Endo M, Omae K, Mori K, Yamamoto N, Tanuma A, Takahashi T (2017) Skeletal muscle depletion during chemotherapy has a large impact on physical function in elderly Japanese patients with advanced non-small-cell lung cancer. BMC Cancer 17(1):571. https://doi.org/10.1186/s12885-017-3562-4
3. Naito T, Okayama T, Aoyama T, Ohashi T, Masuda Y, Kimura M, Shiozaki H, Murakami H, Kenmotsu H, Taira T, Ono A, Wakuda K, Imai H, Oyakawa T, Ishii T, Omori S, Nakashima K, Endo M, Omae K, Mori K, Yamamoto N, Tanuma A, Takahashi T (2017) Unfavorable impact of cancer cachexia on activity of daily living and need for inpatient care in elderly patients with advanced non-small-cell lung cancer in Japan: a prospective longitudinal observational study. BMC Cancer 17(1):800. https://doi.org/10.1186/s12885-017-3795-2
4. Crawford J, Prado CM, Johnston MA, Gralla RJ, Taylor RP, Hancock ML, Dalton JT (2016) Study design and rationale for the phase 3 clinical development program of Enobosarm, a selective androgen receptor modulator, for the prevention and treatment of muscle wasting in Cancer patients (POWER trials). Curr Oncol Rep 18(6):37. https://doi.org/10.1007/s11912-016-0522-0
5. Temel JS, Abernethy AP, Currow DC, Friend J, Duus EM, Yan Y, Fearon KC (2016) Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. Lancet Oncol 17(4):519–531. https://doi.org/10.1016/s1470-2045(15)00558-6
6. Fearon K, Argiles JM, Baracos VE, Bernabei R, Coats A, Crawford J, Deutz NE, Doehner W, Evans WJ, Ferrucci L, Garcia JM, Gralla RJ, Jatoi A, Kalantar-Zadeh K, Lainscak M, Morley JE, Muscaritoli M, Polkey MI, Rosano G, Rossi-Fanelli F, Schols AM, Strasser F, Vellas B, von Haehling S, Anker SD (2015) Request for regulatory guidance for cancer cachexia intervention trials. J Cachexia Sarcopenia Muscle 6(4):272–274. https://doi.org/10.1002/jcsm.12083
7. Baracos VE (2015) Skeletal muscle anabolism in patients with advanced cancer. Lancet Oncol 16(1):13–14. https://doi.org/10.1016/S1470-2045(14)71185-4
8. Kazemi-Bajestani SM, Becher H, Fassbender K, Chu Q, Baracos VE (2014) Concurrent evolution of cancer cachexia and heart failure: bilateral effects exist. J Cachexia Sarcopenia Muscle 5(2):95–104. https://doi.org/10.1007/s13539-014-0137-y
9. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B, Waggoner AD, Houston T, Oslo N, Phoenix A, Nashville T, Hamilton OC, Uppsala S, Ghent LB, Cleveland O, Novara I, Rochester M, Bucharest R, St. Louis M (2016) Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. https://doi.org/10.1093/ehjci/jew082
10. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 5(6):649–655
11. Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, Tannir NM, Litton JK, Reddy A, Hui D, Dalal S, Massie L, Reddy SK, Bruera E (2013) Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol 31(25):3076–3082. https://doi.org/10.1200/JCO.2012.44.4661
12. Stenton C (2008) The MRC breathlessness scale. Occup Med (Lond) 58(3):226–227. https://doi.org/10.1093/occmed/kqm162
13. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, Murphy R, Ghosh S, Sawyer MB, Baracos VE (2013) Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 31(12):1539–1547. https://doi.org/10.1200/JCO.2012.45.2722
14. Fulster S, Tacke M, Sandek A, Ebner N, Tschope C, Doehner W, Anker SD, von Haehling S (2013) Muscle wasting in patients with chronic heart failure: results from the studies investigating comorbidities aggravating heart failure (SICA-HF). Eur Heart J 34(7):512–519. https://doi.org/10.1093/eurheartj/ehs381
15. Bekfani T, Pellicori P, Morris DA, Ebner N, Valentova M, Steinbeck L, Wachter R, Elsner S, Sliziuk V, Schefold JC, Sandek A, Doehner W, Cleland JG, Lainscak M, Anker SD, von Haehling S (2016) Sarcopenia in patients with heart failure with preserved ejection fraction: impact on muscle strength, exercise capacity and quality of life. Int J Cardiol 222:41–46. https://doi.org/10.1016/j.ijcard.2016.07.135
16. Pina IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, Fletcher BJ, Fleg JL, Myers JN, Sullivan MJ (2003) Exercise and heart failure: a statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation 107(8):1210–1225
17. Cramer L, Hildebrandt B, Kung T, Wichmann K, Springer J, Doehner W, Sandek A, Valentova M, Stojakovic T, Scharnagl H, Riess H, Anker SD, von Haehling S (2014) Cardiovascular function and predictors of exercise capacity in patients with colorectal Cancer. J Am Coll Cardiol 64(13):1310–1319. https://doi.org/10.1016/j.jacc.2014.07.948
18. Kazemi-Bajestani SM, Becher H, Ghosh S, Montano-Loza AJ, Baracos VE (2016) Concurrent depletion of skeletal muscle, fat, and left ventricular mass in patients with cirrhosis of the liver. J Cachexia Sarcopenia Muscle 7(1):97–99. https://doi.org/10.1002/jcsm.12093
19. Stewart GD, Skipworth RJ, Fearon KC (2006) Cancer cachexia and fatigue. Clin Med (Lond) 6(2):140–143
20. Mucke M, Mochamat CH, Peuckmann-Post V, Minton O, Stone P, Radbruch L (2016) Pharmacological treatments for fatigue associated with palliative care: executive summary of a Cochrane

collaboration systematic review. J Cachexia Sarcopenia Muscle 7(1):23–27. https://doi.org/10.1002/jcsm.12101

21. Alesi ER, del Fabbro E (2014) Opportunities for targeting the fatigue-anorexia-cachexia symptom cluster. Cancer J 20(5):325–329. https://doi.org/10.1097/ppo.0000000000000065
22. LeBlanc TW, Nickolich M, Rushing CN, Samsa GP, Locke SC, Abernethy AP (2015) What bothers lung cancer patients the most? A prospective, longitudinal electronic patient-reported outcomes study in advanced non-small cell lung cancer. Support Care Cancer 23(12):3455–3463. https://doi.org/10.1007/s00520-015-2699-4
23. Iyer S, Roughley A, Rider A, Taylor-Stokes G (2014) The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. Support Care Cancer 22(1):181–187. https://doi.org/10.1007/s00520-013-1959-4
24. Ripamonti C (1999) Management of dyspnea in advanced cancer patients. Support Care Cancer 7(4):233–243
25. Colin-Ramirez E, Castillo-Martinez L, Orea-Tejeda A, Asensio Lafuente E, Torres Villanueva F, Rebollar Gonzalez V, Narvaez David R, Dorantes Garcia J (2006) Body composition and echocardiographic abnormalities associated to anemia and volume overload in heart failure patients. Clin Nutr 25(5):746–757. https://doi.org/10.1016/j.clnu.2006.01.009