HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2015 July 27.

Published in final edited form as:

Bone Marrow Transplant. 2014 October ; 49(10): 1330–1336. doi:10.1038/bmt.2014.159.

Cardiopulmonary exercise testing prior to myeloablative allo-SCT: a feasibility study

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Abstract

The feasibility of symptom-limited cardiopulmonary exercise testing (CPET) prior to allo-SCT was assessed in addition to the prognostic value of CPET-derived measures. CPET was performed prospectively on 21 patients with hematologic malignancies, with assessments of peak (for example, peak oxygen consumption, VO_{2peak}) and submaximal (for example, ventilatory threshold (VT)) measures of cardiopulmonary function. No serious adverse events were observed during CPET procedures, with 95% of patients achieving criteria for a peak test. Mean VO_{2peak} was 24.7±6.4 mL $kg^{-1}min^{-1}$ (range: 10.9–35.5), equivalent to 29%±17% below that of age-matched healthy controls. All patients proceeded with the conditioning regimen followed by allo-SCT. Median follow-up was 25 months. During this period, 11 (52.4%) patients died (n = 6, relapsed disease; n = 5, non-relapse mortality (NRM)); 9 patients (43%) developed pulmonary toxicity. In univariate analyses, both peak and submaximal markers of cardiopulmonary function were predictors of OS, pulmonary toxicity and NRM. For OS, the HR for VO_{2peak} and VT were 0.89 (95% CI, 0.8–0.99, P = 0.04) and 0.84 (95% CI, 0.71–0.98, P = 0.03), respectively. In conclusion, CPET is safe and feasible prior to allo-SCT. Patients have marked impairments in cardiopulmonary function prior to allo-SCT. CPET-derived metrics may complement conventional measures to improve risk stratification.

INTRODUCTION

Myeloablative conditioning followed by allo-SCT is the only treatment option in many circumstances that provides long-term survival for high-risk or relapsed hematologic malignancies. Nevertheless, these procedures are associated with substantial morbidity and an 18–46% risk of 1-year NRM.[1–4] The incidence of pulmonary toxicity, including interstitial pneumonitis, infectious pneumonia, diffuse alveolar hemorrhage, obstructive bronchiolitis, and respiratory failure requiring ventilatory support, is particularly prevalent

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CONFLICT OF INTEREST

The authors declare no conflict of interest

following myeloablative conditioning regimens, including those in which TBI is utilized.[5–9] Thus, identifying patients at highest risk of transplant-related complications is of major clinical importance.

In clinical practice, the risk of transplant-associated morbidity is evaluated via subjective assessment of physical functioning by performance status measures, age, as well as objective metrics of cardiac and pulmonary function using resting assessments of left ventricular ejection fraction (LVEF) and pulmonary function tests including forced expiratory volume in one second (FEV_1) and carbon monoxide diffusing capacity (D_LCO). Both LVEF and FEV_1 provide valuable prognostic information prior to transplant.[10–14] However, since these measurements are conducted under resting conditions, and do not provide a global measure of cardiopulmonary function and/or reserve capacity under stress conditions, their ability to discriminate patients at high risk of complications may be limited.[15,16] Global cardiopulmonary function reflects the integrative capacity of the cardiovascular and musculoskeletal system to transport and utilize oxygen (O_2) for ATP resynthesis.[17] The efficiency of O_2 transport and utilization determines an individual's exercise capacity. An incremental cardiopulmonary exercise test (CPET) with gas exchange measurement provides the gold standard assessment of peak and submaximal parameters of exercise capacity.[18]

In recent years, our group has shown that CPET is a safe and feasible tool to provide an objective assessment of exercise capacity in select cancer populations.[19–22] In addition, these studies demonstrate that cancer patients have significant and marked reductions in peak (for example, peak oxygen consumption, VO_{2peak}) and submaximal (for example, ventilatory threshold (VT), minute ventilation–carbon dioxide production relationship (VE/VCO_2), OUES) measures of cardiopulmonary function (also commonly referred to as exercise capacity) across the entire survivorship continuum.[20–22] In scenarios where CPET is not available, six-minute walk testing (6MWT) provides a complementary method that provides an assessment of functional capacity. 6MWTs are simple and clinically feasible tests designed to provide an objective measure of exercise capacity in severely deconditioned clinical populations (for example, heart failure, chronic obstructive pulmonary disease and organ transplant recipients). We, and others, have demonstrated the utility of 6MWT in select cancer populations.[23,24] Few studies have evaluated CPET prior to myeloablative allo-SCT.[25]

Against this background, we conducted a pilot study to evaluate the feasibility and safety of symptom-limited CPET and 6MWT in patients with high-risk or relapsed hematologic malignancies, after delivery of conventional chemotherapy, but prior to TBI-based myeloablative conditioning and allo-SCT. Secondary aims were to (1) evaluate pre-transplant conditioning peak and submaximal cardiopulmonary function and functional capacity, and (2) prospectively explore whether these parameters were predictors of post-transplant clinical outcomes. We hypothesized that CPET would be safe and feasible and that CPET-derived parameters and functional capacity would be markedly impaired prior to TBI-based myeloablative conditioning (relative to age-matched normative values) and predictive of select post-transplant clinical outcomes.

MATERIALS AND METHODS

Study participants and setting

Patients with histologically confirmed hematologic malignancies undergoing TBI-based conditioning followed by allo-SCT at Duke University Medical Center (DUMC), Durham, NC, USA, were recruited. Additional eligibility criteria included (1) chemotherapy responsive disease, (2) legal age (>18 years old), (3) ECOG performance status of 0 or 1, (4) primary attending oncologist approval, (5) ability to read and understand English, and (6) no contraindications to a maximal CPET or 6MWT as per American Thoracic Society (ATS) recommendations.[18,26] All patients completed a standard pre-transplant work-up prior to registration involving complete history and physical examination including oxygen saturation, performance status (ECOG), resting FEV_1, D_LCO and LVEF. The DUMC institutional review board approved this study and written informed consent was obtained from all participants prior to initiation of study procedures.

Incremental CPET

To determine peak and submaximal markers of exercise capacity, a CPET with 12-lead ECG monitoring (Mac® 5000, GE Healthcare, Pittsburgh, PA, USA) was performed by certified exercise physiologists prior to initiation of the myelablative conditioning regimen, according to CPET guidelines for clinical populations.[18] All tests were performed on an electronically braked cycle ergometer (Lode Inc, Groningen, Netherlands) with breath-by-breath expired gas analysis. Three minutes of resting metabolic data was collected before participants began cycling at 20 W. Workloads were then increased 5–20 W/min until volitional exhaustion or until a symptom limitation was achieved. Peak VO_2 was defined as the highest VO_2 value for a given 30-s interval within the last 60 s of exercise and VT was calculated using standard methods.[27] The minute ventilation–carbon dioxide production relationship (VE/VCO_2 slope) was determined by measuring the slope across the entire duration of the test.[28] Oxygen uptake efficiency slope (OUES) was determined measuring the slope of VO_2 (mL/min) and $\log_{10}VE$ (L/min) across the entire course of exercise.[29] Age-matched normative VO_{2max} data for healthy individuals without a history of cancer were calculated from the equations provided by Fitzgerald *et al.*[30] (women) and Wilson and Tanaka[31] (men), respectively.

Six-minute walk testing

Six-minute walk testing (6MWT) was performed in a measured corridor according to ATS guidelines.[18] Briefly, patients were instructed to walk at their fastest pace and to cover the longest possible distance over 6 min under the supervision of certified exercise specialists. During exercise, oxyhemoglobin saturation (SpO_2) and heart rate were monitored continuously using pulse oximetry (BCI, Hand-Held Pulse Oximeter, Waukesha, WI, USA). Age and sex-predicted six-minute walking distance (6MWD) was calculated from the equation provided by Gibbons *et al.*[32]

Clinical parameters and toxicity

Medical characteristics were abstracted from medical records. Performance status was assessed using the ECOG at the time of consultation for TBI. All post-transplant cardiac and pulmonary complications, graded according to CTCAE v.4.0 criteria, were recorded. Exercise behavior was assessed by the Godin Leisure Time Exercise Questionnaire.[33] Follow-up survival data were obtained through September 2013.

Myeloablative conditioning regimens

All patients received TBI consisting of 1.5–1.65 Gy bid fractions to a total dose of 12–13.5 Gy. The dose to the lungs, corrected for dose heterogeneity, was attenuated to 7–10 Gy in all patients based on pretransplant pulmonary function tests and history of pulmonary disease.

Myeloablative regimens included TBI with CY (60mg/kg on days – 3 and – 2); TBI with etoposide (60 mg/kg on day – 3); TBI with CY (60 mg/kg on days – 3 and – 2) and fludarabine (25 mg/m^2 on days – 4, – 3 and – 2); TBI with fludarabine (160 mg/m^2); TBI with CY (60 mg/kg on day – 2) and etoposide (60 mg/kg on day – 4); or TBI with melphalan (140 mg/m^2), based on the underlying disease.

Statistical analyses

Descriptive statistics were used to assess demographic and medical characteristics of the participants. Level of VO_{2peak} and 6MWD as well as post-transplant clinical outcomes were evaluated as mean ± s.d.

The primary end point of CPET feasibility was defined as $\geqslant$70% of participants able to successfully achieve the criteria for a ‘peak’ test without serious adverse events. The study procedures were performed in the time period between completion of conventional chemotherapy and initiation of the conditioning regimen. For secondary end points, the Cox proportional hazards model was used to determine the univariate relationship between VO_{2peak} and 6MWD, and OS, NRM and time to post-transplant pulmonary toxicity. Survival time was defined as the time between date of transplant and death; for patients remaining alive, survival was censored at the time of last follow-up. NRM was defined as days from transplant to death, with patients who did relapse being censored at the date of relapse while non-relapsing patients were censored at the date of last follow-up. Time to any pulmonary toxicity was defined as days from transplant to first occurrence of any grade pulmonary toxicity. Patients who did not experience toxicity were censored at death or date of last follow-up. The hazard ratio (HR) and 95% confidence intervals were reported, and Kaplan-Meier plots were created for each time-to-event analysis. No adjustments were made for multiple comparisons, as these analyses were done strictly from an exploratory view. A two-sided significance level of 0.05 was used for all statistical tests. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Participant recruitment took place between March 2011 and September 2012. Twenty one (*n* = 21) patients were enrolled and their characteristics are presented in Table 1. The majority

of patients were male (76%), while mean age and weight were 44 ± 11 years (range, 19–59 years) and 87 ±16 kg, respectively. Eastern Cooperative Oncology Group (ECOG) performance status was 0 (86%) or 1 (14%). The number of chemotherapy courses prior to the conditioning regimen was 1, 2, 3 and 4 in 19%, 38%, 33% and 10% of patients, respectively (standard induction and consolidation scored as one course). Two patients had previously undergone an autologous SCT (both for multiple myeloma).

Pre-transplant pulmonary co-morbidities included remote history of bacterial pneumonia (*n* = 3), history of viral (*n* = 1) and fungal (*n* = 1) pneumonia during chemotherapy, sleep apnea (*n* = 2), and asthma. One patient had both asthma and sleep apnea. The only cardiac co-morbidity was a case of Wolff-Parkinson-White, incidentally identified. None of the patients had active pulmonary or cardiac issues at the time of transplant.

Feasibility of incremental exercise testing

All patients successfully completed all testing procedures. The majority (95%) of CPETs were considered to be of 'peak' effort given that a respiratory exchange ratio of >1.10 was achieved (Table 2). No serious adverse events were observed during CPET procedures. Two patients developed ST-segment depression during CPET; both were referred for further clinical follow-up and were subsequently cleared for transplant. All patients subsequently completed the prescribed conditioning regimen following by allo-SCT, as scheduled. All patients received standard post-transplant supportive care including immunosuppression. Twenty-nine percent (29%) were meeting national exercise guidelines (i.e., ⩾ 150 min/week of moderate to vigorous intensity exercise) at study entry (prior to TBI-based conditioning).

Peak and submaximal cardiovascular function and functional capacity

For the overall sample, mean VO_{2peak} was 24.7 ± 6.4 mL/kg/min (range: 10.9 to 35.5 mL/kg/min), equivalent to 29 ± 17% below age and sex-predicted sedentary values (Table 2). Mean VO_{2peak} was 25.3 ± 5.9 in patients with ECOG 0 (*n*= 18) and 20.7±9.7 for ECOG 1 (n =3). Mean VO_{2peak} at VT (mL/kg/min), VE/VCO_2 and OUES was 16.2±4.7 mL/kg/min, 33.8±4.7, and 2199 ±749, respectively. Mean 6MWD was 164 m (range, 73–213 m), equivalent to 20±16% below that predicted for age and gender.

Bivariate correlations between VO_{2peak} and pre-transplant FEV_1, DLCO and LVEF were analyzed. FEV_1 was a significant predictor of VO_{2peak} (r = 0.44, P = 0.043) but neither DLCO (r =0.07, P =0.77) nor LVEF (r = 0.22, P = 0.33) was significantly correlated.

Toxicity, NRM and survival

OS—Median follow-up was 25 months. During this period 11 (52.4%) patients died (*n* = 6, relapsed disease; *n* = 5 NRM causes). The median survival time for the entire sample from study entry was 20 months (95% CI, 4 to infiniti months). One-year survival for the entire sample was 61%. Univariate analyses indicated a significant association between the CEPT-derived variables VO_{2peak} (mL/kg/min), VT, and OUES and OS (all P' <0.05, Table 3). ECOG performance status was also associated with OS (HR 12.42, P = 0.007).

Pulmonary toxicity—Pulmonary toxicity developed in 9 (43%) patients after transplant, including 3 patients with lethal pulmonary toxicity (grade 5) and 3 additional patients requiring intubation (grade 4) (Table 4). Pulmonary toxicity occurred within 90 days of transplant in 6 patients (4/6 with grade 3–5 toxicity) and later than 90 days in 5 patients (3/5 with grade 3–5 toxicity). Two patients with grade 1–2 acute pulmonary toxicity developed grade 4–5 late pulmonary toxicity. The median time to toxicity was 409 days (range, 12–877).

The 1-year risk of pulmonary toxicity was 35%. In univariate analyses, VO_{2peak} (mL/kg/min), VT and OUES predicted pulmonary toxicity (all $P < 0.05$; Table 3); VE/VCO_2 approached significance ($P = 0.08$).

Cardiac toxicity—One patient developed sinus tachycardia requiring a beta-blocker (grade 2). One patient developed atrial fibrillation while intubated, requiring both medication and DC cardioversion with resolution (grade 3).

Non-relapse mortality—NRM occurred in 5 (24%) patients. Causes of NRM were multi-organ failure ($n = 2$), respiratory arrest, systemic fungal infection and graft failure with sepsis. The 1-year risk of NRM was 23%. VT was the only univariate predictor of NRM (HR 0.72, 95% CI 0.54–0.95, $P = 0.02$) though LVEF was associated with a strong trend (HR 0.01, 95% CI 0–3.71, $P = 0.065$) (Table 3).

DISCUSSION

Myeloablative conditioning followed by allo-SCT is an established treatment modality in high-risk or relapsed hematologic malignancies and often provides the only chance of long-term disease control. Myeloablative conditioning regimens, however, have a major downside characterized by the high incidence of morbidity and NRM.[1–4] Hence, selection of patients for these procedures is a critical clinical decision-making process.

To this end, we found that CPET is a feasible and safe procedure to provide an objective measure of exercise capacity in patients with high-risk or relapsed hematologic malignancies. This is an important finding since CPET procedures require exercise to symptom limitation (volitional exhaustion). Further, CPET was performed within a ‘high-risk’ window between completion of conventional chemotherapy and initiation of the conditioning regimen of TBI and high-dose chemotherapy. No serious adverse events were observed, which is consistent with prior work in non-cancer clinical populations, which report a serious adverse rate during maximal exercise testing of 0.5 per 100 000 tests in healthy individuals and two-to-five per 100 000 tests in patients with cardiovascular disease.[34–36]

Despite the small sample size, we found that both measures of peak O_2 uptake (mL/kg/min and L/min) were consistent prognostic markers of post-transplant clinical outcomes. Similar findings were reported by Wood *et al.*[25] who evaluated CPET in 29 patients with hematologic malignancies undergoing autologous and allogeneic (myeloablative and non-myeloablative) transplants. Few studies have examined the prognostic value of VO_{2peak} in

the oncology setting. Our group found that VO_{2peak} was a strong independent predictor of death in 398 surgical candidates with NSCLC after adjustment for performance status, age, gender and pulmonary function.[21] In further work, we found that VO_{2peak} was an independent predictor of OS in 52 metastatic breast cancer patients. In this setting, a $VO_{2peak} \geqslant 15$ mL/kg/min was associated with a 41% reduction in the risk of death, compared with < 15 mL/kg/min.

The majority of studies examining the prognostic value of CPET have largely focused on the value of VO_{2peak}—a global measure of the integrative capacity of the pulmonary, cardiovascular, neuropsychologic and skeletal muscle systems to deliver and utilize O_2 during a test to symptom limitation. However, other parameters (for example, VT, VE/VCO_2 and OUES) assessed at submaximal or peak workloads can provide further diagnostic, prognostic and clinical decision-making processes. For example, VT estimates the onset of metabolic acidosis caused by an increase in lactate acid production. VT may be particularly valuable in clinical populations since it may more accurately reflect intensities of normal activities of living, and VT can be measured in the majority of subjects during CPET (that is, it is effort-independent). In this study, the prognostic value of VT was particularly robust; indeed, it was the only CPET variable to approach significance in adjusted analyses, though with a larger sample size the other variables may also be prognostic. While traditional CPET metrics such as VO_{2peak} provide a global measure of the peak integrative capacity of O_2 transport/utilization systems, use of other CPET metrics provides distinct but complementary information regarding potential mechanisms of exercise limitation. Because of this, CPET may be able to provide population-specific prognostic information wherein the use and measurement of specific CPET parameters are selected based upon the oncology setting.

Our findings may have important implications for patient selection and risk stratification in the setting of myeloablative conditioning followed by allo-SCT. In current practice, a patient's physiological capacity to withstand and recover from myeloablative conditioning is evaluated using conventional measures such as LVEF and FEV_1. However, resting lung and cardiac function, in contrast to exercise-based measures such as CPET, does not serve to assess the integrative nature of cardiovascular function, assess cardiovascular reserveor reliably predict functional capacity. More sensitive measures may be especially important among patients deemed to have 'good' exercise capacity on the basis of conventional metrics (for example, ECOG 0–1, LVEF > 55% and FEV1 > 70% of predicted). In these scenarios, conventional measures exhibit ceiling effects that do not adequately discriminate patient risk. In this small feasibility study, the lack of prognostic value of the 6MWT suggests that this is also the case for this assessment. Cardiac exercise stress imaging has been shown to be prognostic in the transplant setting.[14] However, this is not analogous to CPET since cardiac exercise stress testing does not provide a measure of exercise capacity or global cardiovascular function.

CEPT and other exercise-based measures are used extensively in non-oncology clinical practice to facilitate treatment eligibility decisions. The only standard clinical application of CPET in the oncology setting is to determine the operability of surgical candidates with lung cancer.[37–40] We contend that myeloablative conditioning followed by allo-SCT is another

relevant setting in which the integration of CPET procedures is indicated. Clearly, in order to support such recommendations, larger adequately powered prospective studies that systematically evaluate the clinical utility and prognostic importance of CPET in allo-SCT are urgently required.

The findings of this study add to the growing body of evidence demonstrating that cancer patients have significant and marked reductions in VO_{2peak}, compared to that predicted for age–sex-matched *sedentary* norms.[17] It is important to note that such reductions were observed in the context of acceptable cardiac and pulmonary function as assessed by LVEF and FEV_1. The marked reductions together with the prognostic value create a strong rationale to investigate the efficacy of interventions to improve cardiopulmonary function in the interval leading up to transplant. A wealth of studies has provided unequivocal evidence that structured aerobic exercise training is arguably one of the most effective strategies to improve cardiopulmonary function in humans.[41] The few studies that have investigated the role of structured exercise training in the transplant setting provide promising evidence that exercise training is a safe and feasible strategy that may lead to improvements cardiopulmonary function and select patient-reported outcomes.[42] These studies, together with the results of our feasibility trial, provide a platform to launch second-generation studies designed to investigate the value of carefully designed exercise interventions on post-transplant morbidity and mortality.

This study has important limitations. Foremost is the potential for selection bias. Our patient population was fairly robust with good performance status and no active cardiopulmonary disease. Clearly, symptom-limited CPETs are only appropriate for patients who are considered to be able to tolerate such tests. In addition, we recruited a small and heterogeneous population with multiple hematologic malignancies, diverse prior cancer treatments, stem cell sources and high-dose chemotherapy regimens combined with TBI. Whether our results are applicable in patients receiving a non-TBI-based preparative regimen is unknown. Furthermore, CPETs require specialized personnel and equipment, as well as medical supervision. As such, the application of CPET in the setting of transplant is likely limited to patients treated at a center with the ability to conduct such testing. Finally, the small number of patients precluded multivariate analyses correcting for variables such as pre-transplant co-morbidities, pulmonary and cardiac function and performance status. Larger prospective trials in homogenous populations will further clarify the utility of CPET procedures in this setting.

In summary, symptom-limited CPET is feasible and safe in patients proceeding with myeloablative allogenic SCT. CPET-derived peak and sub-maximal measures of cardiopulmonary function are also predictors of post-transplant prognosis that may complement conventional pre-transplant physiological measures to improve risk stratification as well as inform decision-making in allo-SCT.

Acknowledgments

LWJ is supported in part by research grants from the National Cancer Institute.

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Table 1

Characteristics of the participants (*n*=21)

Variable	*No. (%)*	*Mean ± s.d.*	*Median (range)*
Age (years)		44 ± 11	48 (19–59)
Female	5 (24)		
Hemoglobin			11 (7.9–15.2)
Weight (kg)		87 ± 16	85 (50–122)
BMI (kg/m^2)		28 ±4	28 (20–38)
ECOG performance status			
0	18 (86)		
1	3 (14)		
Hematopoietic cell transplantation-specific comorbidity index			3 (0–5)
Previous chest RT	4 (19)		
Initial diagnosis			
ALL	7 (33)		
AML	5 (24)		
MDS	1 (5)		
Lymphoma	6 (29)		
Myeloma	2 (10)		
Conditioning chemotherapy with TBI			
CYC	4 (19)		
VP-16	8 (38)		
Fludarabine	7 (33)		
Melphalan	2 (10)		
Cell type			
PBPC	14 (67)		
Cord	7 (33)		
Acute GVHD Glucksburg (overall)			
0	16 (76)		
1	1 (5)		
2	4 (19)		
Related	8 (38)		
Remission	13 (62)		
Hemoglobin, g/L		10.6 ± 1.8	11 (7.9–15.2)
TBI total dose (Gy)		13.2 ± 0.6	13.5 (12–13.5)
TBI fraction size (Gy)		1.5 ± 0.03	1.5 (1.5–1.7)
No. of fractions		8.8 ± 0.4	9 (8–9)
Cardiac/pulmonary function			
FEV_1 (%)		90.1 ± 15.5	96 (64–112)
Corrected D_LCO (%)		79.8 ± 17.9	81 (49–120)

Variable	*No. (%)*	*Mean ± s.d.*	*Median (range)*
LVEF, %[a]		57 ± 6	56 (45–73)
Comorbid conditions			
Cardiac	1 (5)		
Pulmonary	7 (33)		
Hypertension	5 (24)		
Dyslipidemia/hyperlipidemia	5 (24)		
Type 2 diabetes	1 (5)		
Current smoker	0 (0)		
Osteoarthritis	1 (5)		
Current exercise behavior			
Total exercise (min/week)		305 ± 211	220 (40–715)
Meeting ACSM guidelines	6 (29)		

Abbreviations: ACSM = American College of Sports Medicine; D_LCO = diffusing capacity of the lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; FEV_1 = forced expiratory volume in one second; LVEF = left ventricular ejection fraction; MDS = myelodysplastic syndrome; PBPC = PB progenitor cell mobilization; RT = radiation therapy. Continuous variables are reported as mean ± s.d. and categorical variables are reported as *n* (%).

[a]Only one patient had an LVEF <50%.

Table 2

Exercise and functional capacity testing data (n =21)

Variable	*Mean (s.d.)*	*Median (range)*
Resting data		
Heart rate, beats/min	96.7 ± 14.8	91 (73–125)
Systolic blood pressure, mm Hg	121.2 ± 14.8	120 (94–166)
Diastolic blood pressure, mm Hg	76.4 ± 8.1	78 (60–90)
CPET data		
Heart rate, beats/min	178.9 ± 13	181 (150–203)
Systolic blood pressure, mm Hg	171.7 ± 27	168 (136–260)
Diastolic blood pressure, mmHg[a]	76.4 ± 12.1	76 (57–100)
VO_{2peak}, mL/kg/min	24.7 ± 6.4	24.7 (10.9–35.5)
VO_{2peak}, mL/kg/min predicted %	71 ± 17	67 (31–98)
VO_{2peak}, L/min	2.1 ± 0.6	2.0 (1.2–3.5)
VO_{2peak} at VT, mL/kg/min	16.4 ± 5.5	16.9 (6.9–32.1)
VE/VCO_2 slope	33.8 ± 4.7	33.9 (25.9–41.9)
OUES	2199 ± 749	2039 (1216–4143)
Workload (Watts)	154.8 ± 52.6	155 (65–255)
METs	11.0 ± 4	11 (3.1–20)
RER	1.2 ± 0.09	1.2 (1.0–1.4)
RER $\geqslant$ 1.10, no. (%)	20 (95)	
6MWT data		
6MWD, m	163.6 ±32.5	164.6 (73.2–213.4)
6MWD, predicted %	80 ± 16	82 (37–109)

Abbreviations: CPET = cardiopulmonary exercise test; METs = metabolic equivalents; 6MWT = six-minute walk test; 6MWD = six-minute walk distance; OUES = oxygen uptake efficiency slope; RER = respiratory exchange ratio; SpO_2 = oxygen saturation; VE/VCO_2 = minute ventilation–carbon dioxide production relationship; VO_{2peak} = peak oxygen consumption; VT = ventilatory threshold. Data are presented as mean ± s.d. for continuous data and n (%) for categorical data.

[a]One patient was removed due to apparent data entry error.

Table 3

Unadjusted time-to-event analysis for pre-transplant CPET-derived parameters, functional capacity and standard metrics

Predictor Time-to-event variable	*Estimate (SE)*	*Hazard ratio (95% CI)*	*P-value*
OS			
CPET-derived maximal variables			
VO_{2peak}, mL/kg/min	− 0.113 (0.054)	0.89 (0.80 to 0.99)	0.035
VO_{2peak}, L/min	− 1.018 (0.532)	0.36 (0.13 to 1.03)	0.055
CPET-derived submaximal variables			
VT	− 0.178 (0.083)	0.84 (0.71 to 0.98)	0.032
OUES	− 0.001 (0.001)	0.99 (0.99 to 1.00)	0.016
VE/VCO_2	0.113 (0.072)	1.12 (0.97 to 1.29)	0.117
Functional capacity			
6MWD	− 0.012 (0.008)	0.98 (0.97 to 1.00)	0.139
Standard metrics			
Age	0.035 (0.032)	1.04 (0.97 to 1.10)	0.274
LVEF	−0.087 (0.070)	0.92 (0.8 to 1.05)	0.217
FEV_1	−0.021 (0.019)	0.98 (0.94 to 1.02)	0.256
Corrected D_LCO (%)	−0.035 (0.021)	0.97 (0.93, 1.01)	0.101
ECOG	2.519 (0.928)	12.42 (2.01 to 76.63)	0.007
Pulmonary toxicity			
CPET-derived maximal variables			
VO_{2peak}, mL/kg/min	− 0.122 (0.060)	0.89 (0.79 to 0.99)	0.040
VO_{2peak}, L/min	− 1.139 (0.604)	0.32 (0.09 to 1.05)	0.059
CPET-derived submaximal variables			
VT	− 0.257 (0.097)	0.77 (0.64 to 0.94)	0.008
OUES	− 0.002 (0.001)	0.99 (0.99 to 1.00)	0.019
VE/VCO_2	0.138 (0.078)	1.15 (0.98 to 1.34)	0.079
Functional capacity			
6MWD	− 0.011 (0.009)	0.99 (0.97 to 1.01)	0.205
Standard metrics			
Age	0.009 (0.031)	1.01 (0.95 to 1.07)	0.775
LVEF	− 0.054 (0.067)	0.95 (0.83 to 1.08)	0.415
FEV_1	− 0.007 (0.022)	0.99 (0.95 to 1.04)	0.744
Corrected D_LCO (%)	− 0.012 (0.020)	0.99 (0.95, 1.03)	0.545
ECOG	0.558 (1.120)	1.75 (0.19 to 15.71)	0.618
Non-relapse mortality			
CPET-derived maximal variables			
VO_{2peak}, mL/kg/min	− 0.115 (0.074)	0.89 (0.77 to 1.03)	0.121
VO_{2peak}, L/min	− 0.778 (0.741)	0.46 (0.11 to 1.96)	0.294
CPET-derived submaximal variables			

Predictor Time-to-event variable	*Estimate (SE)*	*Hazard ratio (95% CI)*	**P-*value***
VT	− 0.333 (0.146)	0.72 (0.54 to 0.95)	0.022
OUES	− 0.001 (0.001)	0.99 (0.99 to 1.00)	0.136
VE/VCO_2	0.009 (0.106)	1.01 (0.82 to 1.24)	0.930
Functional capacity			
6MWD	− 0.012 (0.013)	0.99 (0.96 to 1.01)	0.349
Standard metrics			
Age	− 0.007 (0.037)	0.993 (0.92 to 1.07)	0.857
LVEF	− 0.218 (0.118)	0.80 (0.64 to 1.01)	0.065
FEV_1	0.004 (0.032)	1.00 (0.94 to 1.07)	0.891
Corrected D_LCO (%)	0.003 (0.027)	1.00 (0.95, 1.06)	0.907
ECOG	1.763 (1.414)	5.83 (0.37 to 93.25)	0.213

Abbreviations: CPET = cardiopulmonary exercise test; D_LCO = carbon monoxide diffusing capacity; ECOG = Eastern Cooperative Oncology Group; FEV_1 = forced expiratory volume in one second; LVEF = left ventricular ejection fraction; 6MWD = six-minute walk distance; OUES = oxygen uptake efficiency slope; VE/VCO_2, minute ventilation–carbon dioxide production relationship; VO_{2peak} = peak oxygen consumption; VT = ventilatory threshold.

Table 4

Post-transplant pulmonary toxicity

Timing	n	*Details*
Acute (< 90 days)		
Grade 1	2	Self-limiting mild cough/dyspnea
Grade 2	0	
Grade 3	1	Dyspnea and hypoxia requiring temporary oxygen use
Grade 4	2	Dyspnea requiring intubation[a]
Grade 5	1	Hypoxia, pulmonary hemorrhage, ARDS, recurrent pulmonary Rhizopus
Late (≥90 days)		
Grade 1	0	
Grade 2	2	Moderate dyspnea and cough[b]
Grade 3	0	
Grade 4	1	Hypoxemia requiring intubation (possible infection)
Grade 5	2	Respiratory failure from fungal infection (n = 1) and ARDS with diffuse alveolar hemorrhage (n = 1)

Abbreviations: ARDS = acute respiratory distress syndrome.

[a] Suspected pneumonitis in one patient; unclear etiology in one patient.

[b] Enterovirus, rhinovirus and aspergillus documented at bronchoscopy (n = 1); diffuse interstitial infiltrates and hypoxia with ambulation treated for presumed pneumocystis carinii pneumonia.