CNS disease should receive routine CSF surveillance and IT chemotherapy.

There are several limitations of this study. In an effort to conduct the survey anonymously, we were unable to link individual respondents to their specific institutions, perhaps leading to some degree of redundancy should some centers be disproportionately represented. There may also have been selection bias among the 41% of physicians who completed the survey with respect to centers. Finally, the multiple-choice format of the survey likely oversimplifies the nuance involved in routine surveillance practices among practitioners. The single-center review was limited somewhat by heterogeneity of disease subtype and conditioning regimen as well as sample size.

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Cardiovascular Function in Long-Term Hematopoietic Cell Transplantation Survivors

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A B S T R A C T

Peak oxygen consumption (VO_{2peak}), as measured by cardiopulmonary exercise testing (CPET), is a powerful independent predictor of cardiovascular disease (CVD) and all-cause mortality in a broad range of populations. We assessed the safety and feasibility of CPET in aging long-term hematopoietic cell transplantation (HCT) survivors, a population at high risk for premature onset of CVD. Next, we examined how organ-specific impairments (eg, cardiac, pulmonary, hematologic) impact VO_{2peak} after HCT. Twenty consecutive HCT survivors underwent a comprehensive assessment of cardiopulmonary health that included CPET, echocardiography with strain, pulmonary function testing, 6-minute walk test, and timed up and go. Median age at assessment was 67.4 years (range, 42 to 75), and median time from HCT was 9.8 years (range, 3 to 20). No adverse events were observed during CPET procedures, and 95% of studies were considered to be at "peak" effort (respiratory exchange ratio ≥ 1.10). VO_{2peak} was on average 22% less than predicted, and allogeneic HCT survivors had markedly lower VO_{2peak} when compared with autologous HCT survivors (18.2 mL/kg/min versus 22.2 mL/kg/min; $P = .05$). Six participants (30%) had $VO_{2peak} \leq 16$ mL/kg/min, a threshold associated with a 9-fold

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risk of death in patients undergoing HCT. Despite the presence of normal (>50%) resting left ventricular ejection fraction in all participants, 25% had markedly abnormal left ventricular longitudinal strain, an advanced echocardiographic measure of myocardial dysfunction. These findings highlight the role of stress-based measures and advanced myocardial imaging to characterize CVD risk in HCT survivors, setting the stage for tailored interventions to prevent CVD with its attendant morbidity and mortality.

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INTRODUCTION

Currently, an estimated > 160,000 hematopoietic cell transplantation (HCT) survivors are living in the United States, and that number is expected to exceed 500,000 by the year 2030 [1,2]. In this population, cardiovascular diseases (CVDs) such as myocardial infarction, heart failure, and stroke are leading causes of late-occurring morbidity and mortality [3]. HCT survivors have a 4-fold higher risk of developing CVD when compared with the general population [4]; median age at first cardiovascular event such as myocardial infarction is 53 years (range, 35 to 66) [5], which is much lower than would be expected in the general population (67 years) [6]. The increased risk of CVD, coupled with the recognition that these complications develop earlier than would be expected in the general population, has raised the possibility of an accelerated cardiovascular aging phenotype in HCT survivors [3].

The cardiovascular system has an inherent reserve capacity (cardiovascular reserve capacity), which is maintained by cross-organ systems (cardiac, pulmonary, hematologic, musculoskeletal) that adapt to physiologic and/or pathologic perturbations [7,8]. However, this reserve capacity is finite; chronic pathologic perturbations to 1 or more of the organ systems that maintain its integrity lead to cardiovascular aging [7]. For HCT survivors, depletion of reserve capacity may be initiated by pre-HCT and HCT-related therapeutic exposures and worsened by post-HCT complications such as graft-versus-host disease, comorbidities (eg, hypertension, diabetes), and lifestyle behaviors (deconditioning) [3,9].

Peak oxygen consumption (VO_{2peak}), as measured by cardiopulmonary exercise testing (CPET), is the gold standard measure of aerobic capacity and cardiovascular reserve [10]. VO_{2peak} is a powerful independent predictor of CVD and all-cause mortality in a broad range of populations, including breast and lung cancer patients [10-12]. Two studies [13,14] in HCT patients reported that low VO_{2peak} *before* HCT was associated with increased risk of nonrelapse mortality, independent of other prognostic measures such as age, resting left ventricular (LV) ejection fraction (EF), and HCT comorbidity index. There is a paucity of information regarding VO_{2peak} *after* HCT and how organ-specific perturbations impact cardiovascular reserve capacity in HCT survivors. Addressing this gap in knowledge is especially important for aging long-term HCT survivors, a population at highest risk for premature onset of CVD [3,15]. Accordingly, we evaluated the safety and feasibility of CPET in survivors who were on average 10 years from HCT. Secondary objectives were to assess the level of VO_{2peak} impairment and to examine the impact of organ-specific (eg, cardiac, pulmonary, hematologic) impairments on VO_{2peak} in these survivors. We hypothesized that CPET would be feasible and safe and that detailed assessment of specific organ systems would provide useful information regarding the etiology of VO_{2peak} impairment in long-term HCT survivors.

METHODS

Study Participants

Patients were identified from an existing electronic database of HCT survivors that included information on age at diagnosis, therapeutic exposures, chronic health conditions, and vital status. Two cohorts were targeted (allogeneic and autologous; 10 participants per cohort). Eligibility criteria included ≥2 years from HCT, no evidence of active hematologic malignancy, and HCT for acute leukemia (lymphoblastic, myeloid) or lymphoma (non-Hodgkin, Hodgkin). Survivors with any of the following conditions were ineligible: acute myocardial infarction (within 3 to 5 days of any planned study procedures), unstable angina, uncontrolled arrhythmia causing symptoms or hemodynamic compromise, recurrent syncope, acute myocarditis or pericarditis, symptomatic severe aortic stenosis, uncontrolled heart failure, acute (within 3 months) pulmonary embolus or pulmonary infarction, thrombosis of lower extremities, moderate or severe persistent asthma (as defined by the National Asthma Education and Prevention Program), and acute noncardiopulmonary disorders that may affect exercise performance or be aggravated by exercise (eg, active systemic infection, renal failure, thyrotoxicosis).

Potentially eligible patients were sequentially recruited by mail or in person using a stratified approach to ensure a balanced representation across key risk factors: age at recruitment (<65 years, ≥65 years), sex, and type of HCT (allogeneic, autologous). Final eligibility was determined by a cardiologist who performed a detailed history and physical examination and a resting electrocardiogram. Study participants underwent a comprehensive assessment of cardiopulmonary function that included 2-dimensional echocardiography, symptom-limited CPET, and pulmonary function test (PFT). Participants also performed a 6-minute walk test (6MWT) and timed up and go (TUG) test and provided information regarding their past medical history and a blood sample to measure hemoglobin. The City of Hope institutional review board approved this study, and written informed consent was obtained from all participants prior to initiation of study procedures.

Cardiopulmonary Exercise Testing

The symptom-limited CPET was conducted on an electronically braked cycle ergometer (CareFusion Respiratory Technologies; Yorba Linda, CA) with breath-by-breath expired gas analysis (CareFusion V max Encore). All tests were conducted by 2 certified exercise technicians under the direct supervision of the study pulmonologist (D.H.); testing was conducted per American Thoracic Society guidelines [10,16]. Participants were monitored continuously with a 12-lead electrocardiogram during exercise and 5 minutes of recovery. During exercise, oxyhemoglobin saturation was monitored continuously using finger pulse oximetry, whereas blood pressure was measured by an automated sphygmomanometer every 2 minutes [10]. Three minutes of resting metabolic data were collected before participants began cycling at 20 W. Afterward, workloads were then increased 5 to 20 W/min until volitional exhaustion or until a symptom limitation was achieved. VO_{2peak} was defined as the highest VO_2 value for a given 30-second interval within the last 60 seconds of exercise [17]. Age-matched normative VO_{2peak} data for healthy individuals without a history of cancer were calculated from the established sex-specific equations [18,19].

Acceptable test criteria included any of the following: (1) a peak or plateau in oxygen consumption concurrent with increased power output, (2) a respiratory exchange ratio ≥ 1.1, (3) volitional exhaustion, and (4) a rating of perceived exertion greater than 19 [10,13]. Severe adverse event was defined as the occurrence of at least grade 3 (Common Terminology of Adverse Events, version 4) cardiovascular event: (1) sustained ventricular tachycardia, (2) myocardial ischemia, (3) syncope, (4) provision of cardiac life support medications, (5) direct admission to emergency room/equivalent, or (6) death. Criteria for ischemic changes in electrocardiogram included .1-mV deviation of the ST segment horizontal to or away from the baseline isoelectric line at .08 seconds after the J-point in the absence of significant resting ST-T abnormalities or left bundle branch block [10].

Echocardiogram

Resting 2-dimensional echocardiograms with tissue Doppler strain were performed per the American Society of Echocardiography and the European Association of Cardiovascular Imaging practice guidelines [20]. EF was derived from LV volumes in systole and diastole, measured on M-mode recordings obtained from standard LV parasternal long axis view, using the formula (LV volume in diastole – LV volume in systole / LV volume in diastole) × 100. LV global longitudinal strain (GLS) was measured manually by

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