Quantitative Measures of Physical Functioning After Autologous Hematopoietic Stem Cell Transplantation in Multiple Myeloma: A Feasibility Study

Sascha A. Tuchman,[1] Amy Lane,[2] Whitney E. Hornsby,[2] Caroline Bishop,[2] Samantha Thomas,[2] James E. Herndon, II,[2] Gwynn Long,[1] Cristina Gasparetto,[1] Lee W. Jones[2]

Abstract

Cardiopulmonary exercise testing (CPET) and 6-minute walk testing (6MWT) are important, quantitative measures of physical function, but they have not been tested in patients who have undergone stem cell transplant for multiple myeloma. Twenty-two post-transplant myeloma patients underwent CPET and 6MWT, and assessment of patient-reported outcomes (PROs). Patients had marked reductions in performance on CPET and 6MWT, but no correlation was seen with PROs. Further study is needed to better understand the meaning of this finding of persistently impaired physical function in myeloma patients more than a year post-transplant.

Background: The safety and feasibility of the symptom-limited cardiopulmonary exercise test (CPET) and the 6-minute walk test (6MWT) has not been rigorously tested in patients with multiple myeloma (MM) after high-dose chemotherapy with autologous stem cell transplantation (ASCT), nor have correlations with patient-reported outcomes (PROs) been explored. **Patients and Methods:** We undertook CPET, 6MWT, and PRO assessments using standardized measurements and questionnaires in patients with MM in remission after ASCT. **Results:** A total of 22 patients who were a median of 17 months after ASCT underwent assessment. No severe adverse events were observed. Exercise capacity, measured during CPET as the peak oxygen consumption, was 17.5 $\pm$ 5.9 mL/kg/min, the equivalent of 38% $\pm$ 18% less than that for age- and sex-predicted sedentary normative values. During the 6MWT, the mean 6-minute walk distance was 500 m, or 25% $\pm$ 13% less than the predicted values. Additional analysis using Pearson's correlation revealed no significant univariate associations between exercise or functional capacity and any PROs. **Conclusion:** Patients with MM have marked and significant reductions in quantitative measures of physical function for years after the initial therapy, although that did not correlate with PROs in the present pilot study. Larger prospective studies are required to determine the clinical ramifications of these findings and to mechanistically dissect them, as well to test interventions aimed at mitigating them.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 2, 103-9
Keywords: Cardiorespiratory fitness, Chemotherapy, Exercise tolerance, Multiple myeloma, Transplantation

Introduction

Multiple myeloma (MM) is an incurable cancer of the plasma cells. Currently, conventional cytotoxic drugs, novel agents, high-dose corticosteroids, and high-dose melphalan with autologous hematopoietic stem cell transplantation (ASCT) are the cornerstones of clinical management. The introduction of novel agents such as bortezomib, thalidomide, and lenalidomide has improved the median overall survival from diagnosis from approximately

[1]Duke Cancer Institute, Durham, NC
[2]Duke University Medical Center, Durham, NC

Submitted: Apr 21, 2014; Revised: Aug 27, 2014; Accepted: Sep 17, 2014; Epub: Sep 28, 2014

Address for correspondence: Lee W. Jones, PhD, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 300 East 66th Street, New York, NY 10065
E-mail contact: jonesl3@mskcc.org

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2014.09.002

2.5 years to > 6 years.[1,2] Given these advances and the hence increasing focus on "survivorship" care of patients with MM, the chronic and late effects of MM and associated therapy are becoming increasingly important.

The pathophysiology of MM and the toxicity profile of combination regimens has resulted in a diverse range of potentially debilitating problems such as anemia, fatigue, pain, and peripheral neuropathy.[3,4] Furthermore, the nonspecific effects of therapy such as physical inactivity (i.e., deconditioning)[5] have a marked detrimental effect on physical functioning, which can compromise patient quality of life (QOL) and other patient-reported outcomes (PROs), such as fatigue, and lead to poorer overall survival.[6-8] However, the evaluation of physical functioning using quantitative measures has received scant attention in those with MM; therefore, the precise magnitude of impairment in physical functioning and its associated effect on PROs related to the therapeutic management of MM is not known.

In recent years, our group and others have investigated the safety, utility, and prognostic value of clinical tools that provide an objective assessment of physical functioning in patients with other cancers.[6-9] Overall, the results of these studies have provided promising evidence that (1) objective measures, including a symptom-limited cardiopulmonary exercise test (CPET) and the 6-minute walk test (6MWT), are safe and feasible tools to quantitatively evaluate physical functioning[6-9]; (2) patients with cancer will have, on average, marked impairments in physical function during and years after the completion of primary therapy[10-12]; and (3) these measures might provide important information for risk stratification and prognosis beyond conventional measures of physical functioning (e.g., performance status and evaluation of cardiac and pulmonary function at rest).[13]

Against this background, we conducted a cross-sectional pilot study to examine the safety and feasibility of a single symptom-limited CPET and 6MWT in patients with MM in remission long after recovery from ASCT. A secondary aim was to explore whether these assessments correlated with PROs and select medical characteristics. We hypothesized that CPET and 6MWT would be safe procedures. We also hypothesized that patients with MM would have significant impairments in the objective measures of physical functioning and that such measures would correlate with select PROs and medical characteristics.

Patients and Methods

Patients and Study Design

Patients with histologically confirmed MM after ASCT, who were in remission (i.e., partial response or better according to standard consensus criteria[14]), and being followed up at Duke Cancer Institute, were potentially eligible. Additional major eligibility criteria included (1) ≥ 6 months had passed since ASCT; (2) no known, potentially unstable bony lesions; (3) Karnofsky performance status (KPS) of ≥ 70; (4) primary attending oncologist approval; (5) ability to provide written consent in English; and (6) no contraindications to a CPET or 6MWT, in accordance with the American Thoracic Society (ATS) recommendations.[15] The Duke University Health System institutional review board approved the study, and all participants provided written informed consent before the initiation of the study procedures.

Exercise-Related Serious Adverse Events and Risk Stratification

Serious adverse events (SAEs) were considered any serious event occurring during study activities. On the basis of the medical record review, all participants were categorized into pre-exercise risk stratification categories according to the American College of Sports Medicine (ACSM) recommendations.[16]

Quantitative Measures of Physical Function

The CPET, with 12-lead electrocardiogram (ECG) monitoring (Mac 5000, GE Healthcare), was performed by 2 certified exercise physiologists. The specific protocol for this test has been previously reported in detail.[17] In brief, all tests were performed using an electronically braked cycle ergometer (Lode Inc., Groningen, The Netherlands) with breath-by-breath expired gas analysis. Three minutes of metabolic data at rest were collected before the participants began cycling at 20 W. The workloads were then increased 5 to 20 W/min until volitional exhaustion or until symptom limitation was achieved. The peak oxygen consumption (VO_{2peak}) during CPET was defined as the greatest VO_2 value for a given 30-second interval within the last 60 seconds of exercise, and the submaximal response (ventilatory threshold) was calculated using standard methods.[18] The age-matched normative VO_{2peak} data for healthy individuals without a history of cancer were calculated from the equations provided by Fitzgerald et al.[19] for women, and Wilson and Tanaka[20] for men.

The 6MWT was performed in a measured corridor according to ATS guidelines.[15] In brief, the patients were instructed to walk at their fastest pace and to cover the longest possible distance within 6 minutes under the supervision of certified exercise specialists. During exercise, the oxyhemoglobin saturation and heart rate were monitored continuously using pulse oximetry (BCI, Hand-Held Pulse Oximeter, Waukesha, WI). The age- and sex-predicted 6-minute walk distance (6MWD) was calculated from the equation provided by Gibbons et al.[21]

Patient-Reported Outcomes

The patients' QOL was assessed using the Functional Assessment of Cancer Therapy-General Cancer (FACT-G) scale.[22] The FACT-G contains subscales for physical (7 items), functional (7 items), emotional (6 items), and social and family (7 items) well-being. The MM- and ASCT-specific concerns were assessed using the Bone Marrow Transplantation (BMT) version of the FACT measurement system. The 5 subscales (FACT-G plus BMT) were summed to obtain the FACT-BMT score. Fatigue was assessed using the 13-item fatigue scale of the FACT measurement system developed specifically for the cancer population.[23] Depression, sleep quality, and pain were assessed using the Center for Epidemiological Studies Depression Scale,[24] the Pittsburgh Sleep Inventory,[25] and the Brief Pain Inventory,[26] respectively.

Clinical Parameters and Performance Status

The medical characteristics were abstracted from the medical records. Performance status was assessed using the Karnofsky performance scale (KPS), which was assessed at the subject's last clinic visit before the present study began by the subject's attending oncologist. ASCT-related toxicity was graded according to the