Cumulative Burden of Morbidity Among Testicular Cancer Survivors after Standard Cisplatin-Based Chemotherapy: A Multi-Institutional Study

Sarah L. Kerns[1], Chunkit Fung[1], Patrick O. Monahan[2], Shirin Ardeshir-Rouhani-Fard[2], Mohammad Abu Zaid[2], AnnaLynn M. Williams[1], Tim Stump[2], Howard D. Sesso[3], Darren R. Feldman[4], Robert J. Hamilton[5], David Vaughn[6], Clair Beard[7], Robert Huddart[8], Jeri Kim[9], Christian Kollmannsberger[10], Deepak Sahasrabudhe[1], Ryan Cook[2], Sophie D. Fossa[10], Lawrence Einhorn[2], Lois B. Travis[2] for The Platinum Study Group

[1]University of Rochester Medical Center, [2]Indiana University, [3]Brigham and Women's Hospital, [4]Memorial Sloan Kettering Cancer Center, [5]Princess Margaret Cancer Center, [6]University of Pennsylvania, [7]Dana-Farber Cancer Institute, [8]Royal Marsden Hospital, [9]MD Anderson Cancer Center, [10]University of British Columbia, [10]Oslo University Hospital

Acknowledgment of research support: This work was supported by the National Cancer Institute (1R01 CA157823 to LBT and K07 CA187546 to SLK).

Corresponding Author:
Lawrence H. Einhorn, M.D.
Department of Medical Oncology
Indiana University Melvin and Bren Simon Cancer Center
535 Barnhill Drive RT432
Indianapolis, IN 46202
Email: leinhorn@iupui.edu

Running head: Cumulative Burden of Morbidity among Testicular Cancer Survivors

Prior presentation: Our results were presented in part at the Poster Discussion Session of the 2016 and 2017 ASCO annual meetings in Chicago, Illinois and as an Oral Presentation at the 2016 ASCO Cancer Survivorship Symposium in San Francisco, California.

Disclaimers: None

Abstract

PURPOSE: In this multi-center study, we evaluate for the first time the cumulative burden of morbidity (CBM) among over 1,200 testicular cancer survivors (TCS) and apply factor analysis to determine the co-occurrence of adverse health outcomes (AHOs).

PATIENTS AND METHODS: Participants were ≤55 years at diagnosis, finished first-line chemotherapy ≥1 year previously, completed a comprehensive questionnaire, and underwent physical examination. Treatment data were abstracted from medical records**.** A CBM score encompassed the number and severity of AHOs, with ordinal logistic regression used to assess associations with exposures. Nonlinear factor analysis and the nonparametric DETECT procedure determined which AHOs co-occurred.

RESULTS: Among 1,214 TCS, approximately 20% had a CBM score of high (15%) or very high/severe (4.1%), while almost 80% scored medium (30%) or low/very low (47%). Increased risks of higher scores were associated with 4 cycles of either ifosfamide, etoposide, and cisplatin (VIPX4) (OR=1.96; 95% CI 1.04-3.71) or bleomycin, etoposide, and cisplatin (BEPX4) (OR=1.44; 95% CI 1.04-1.98), older attained age (OR=1.18; 95%CI 1.10-1.26), current disability leave (OR=3.53; 95%CI 1.57-7.95), less-than-college education (OR=1.44; 95%CI 1.11-1.87), and current or former smoking (OR=1.28; 95% CI 1.02-1.63). CBM score did not differ following VIPX4 vs. BEPX4 (p=0.36). Asian race (OR=0.41; 95%CI 0.23-0.72) and vigorous exercise (OR=0.68; 95%CI 0.52-0.89) were protective. Variable-clustering analyses identified six significant AHO clusters (chi-squareP<0.001): (1) hearing loss/damage, tinnitus (OR=16.3); (2) hyperlipidemia, hypertension, diabetes (OR=9.8); (3) neuropathy, pain, Raynaud phenomenon (OR=5.5); (4) cardiovascular and related conditions (OR=5.0); (5) thyroid disease, erectile dysfunction (OR=4.2); and (6) depression/anxiety, hypogonadism (OR=2.8).

CONCLUSIONS: Factors associated with higher CBM may identify TCS in need of closer monitoring. If confirmed, identified AHO clusters could guide the development of survivorship care strategies.

Introduction

The number of cancer survivors has increased markedly in recent decades, with an estimated 18 million in the U.S. by 2022.[1] Given these increasing numbers, it is critical to understand and quantify the late effects of cancer and its treatment to inform survivorship care strategies. An important population in which to assess adverse health outcomes (AHOs) are survivors of testicular cancer (TC), the most common cancer in men age 18-39 years.[2] Since effective cisplatin-based chemotherapy was introduced in the 1970s[3], the overall age-adjusted 5-year relative survival rate is >95%,[4] and survivors remain at risk for decades for the late effects of cancer and its treatment. Characterization of AHOs is facilitated by the homogeneity of treatment regimens. For four decades, therapy for advanced TC has typically consisted of platinum-based chemotherapy. For good-risk disease, standard treatment comprises either 3 cycles of bleomycin, etoposide, and cisplatin (BEPX3) or 4 cycles of etoposide plus cisplatin (EPX4), while for intermediate or poor-risk TC, 4 cycles of BEP (BEPX4) or 4 cycles of etoposide, ifosfamide, and cisplatin (VIPX4) are administered.[5,6] Although treatment for good-risk TC with BEPX3 versus EPX4 results in lower cisplatin exposure, it is accompanied by potential bleomycin side effects.[7] To our knowledge, no study to date has evaluated the cumulative burden of morbidity (CBM) after BEPX4 vs. VIPX4 or after BEPX3 vs. EPX4, taking into account both the number and severity of AHOs. Such characterization is important to develop risk-stratified, evidence-based follow-up recommendations. Moreover, as noted previously,[8] a better understanding of AHOs may help guide TC management, especially in the controversial area of whether good-risk patients should receive EPX4 or BEPX3.

To provide new information about CBM following contemporary cisplatin-based chemotherapy for TC, we examined both the number and severity of AHOs among 1,214 TC survivors (TCS) enrolled in the Platinum Study, a large, multi-center clinical investigation.[9] We evaluated for the first time the co-aggregation of AHOs to identify clusters that co-occur, and identified clinical, sociodemographic, and behavioral factors associated with elevated CBM.

Methods

Study Population

The Platinum Study was approved by each institutional IRB, and all participants provided written informed consent. The cohort was described in detail previously.[2,10] Briefly, eligible TCS had histologic/serological diagnosis of germ cell tumor, were aged ≤55 years at diagnosis, completed first line cisplatin-based chemotherapy ≥1 year previously, and were undergoing routine follow-up at the participating site. All participants are referred to as TCS. At study enrollment, participants reported current prescription medication use with indication, underwent a brief physical examination, and completed comprehensive health questionnaires. Cancer diagnosis and treatment data were abstracted from medical records (see online Appendix-Supplemental Methods). TCS indicated the average time per week participating in various physical activities during the past year.[11,12] These were grouped into vigorous (≥6 METs) and non-vigorous (<6 METS) activities (see online Appendix-Supplemental Methods).[13]

Measurement of Adverse Health Outcomes

Participant responses were mapped to individual AHOs and graded according to severity on a 0-4 scale, using a modified version of the NCI Common Terminology Criteria for Adverse Events (CTCAEv4.03),[14] as in prior studies.[15,16] A multidisciplinary panel of experts agreed on all grades (DS, LBT, CF, HDS, LE, SDF). Supplementary Table 1 lists individual AHOs and grading criteria (see online Appendix-Supplemental Methods).[15,16] If no response was provided (<1%), it was conservatively treated as no symptom/diagnosis. CBM score was calculated based on the number and severity of AHOs, following methods adapted from Geenen et al.[15] (Supplementary Table 2). A secondary CBM score, CBM_{Pt}, was calculated using AHOs previously related to cisplatin exposure, i.e. peripheral sensory neuropathy, autonomic neuropathy, hearing damage, tinnitus, and kidney disease.[17,18]

Statistical Analysis

Discrete and continuous data were described using numbers (percentages) and medians (ranges), respectively. Sociodemographic, health behavior, and treatment variables were individually tested for association with CBM score using student's t-test (continuous variables) or Pearson's chi-square test (categorical variables). Variables were then combined in a multivariable ordinal logistic regression model with CBM score as the dependent variable. Unless otherwise noted, variables with Wald chi-square p-value ≥0.1 in the full model were removed from the final model. In the latter, very high and severe CBM categories were collapsed, given sparse data. Multivariable models that investigated the effect of cumulative cisplatin dose on CBM_{Pt} score included the same covariates as the main model except that chemotherapy regimen was omitted, given its strong correlation with cumulative cisplatin dose.

Ordinal logistic regression examined the relationship between CBM score and self-reported health (the dependent variable). For all ordinal logistic regression models, the assumption of proportionality of odds across response categories was confirmed by comparing the Bayesian Information Criterion (BIC) for the proportional odds model to the BIC from a partial proportional odds model. All descriptive statistics and regression analyses used Stata v14.1 (StataCorp.2015.College Station,TX).

Cluster analysis of variables was performed with non-linear factor analysis and the non-parametric conditional item-pair covariance method of the cross-validated Dimensionality Evaluation To Enumerate Contributing Traits (DETECT) procedure (see online Appendix-Supplemental Methods). Each AHO was dichotomized: grades 0 and 1 were combined; and grades 2, 3 and 4 were combined. Due to sparse numbers, transient ischemic attack and stroke were collapsed into a single AHO; hypertriglyceridemia and hypercholesterolemia were combined into hyperlipidemia. Average item-pair odds ratios (OR) were calculated by averaging the log OR across AHO pairs, and then exponentiating the average value.

Results

Median age at evaluation for 1,214 TCS was 37 years (range,18-74 years) and median time since chemotherapy completion was 4.2 years (range,1-30 years) (**Table 1)**. Of all patients, 1,157 (95.3%) were seen in clinic during routine follow-up care, and approximately 90% completed chemotherapy within 15 years of enrollment. Most participants (N=1,035; 85.3%) received BEPX3 (N=460; 37.9%), BEPX4 (N=222; 18.3%), or EPX4 (N=353; 29.1%); 44 TCS received VIP, typically 4 cycles (n=32). Median cumulative cisplatin dose was 400mg/m^2, with approximately one third receiving 300mg/m^2 (N=447; 36.8%). Retroperitoneal lymph node dissection (RPLND) was performed on 46.3% participants. Most TCS were white (85.3%), married/living as married (61.0%), employed (88.7%), and educated beyond high school (88.3%).

The most prevalent AHOs, of any severity, were obesity (41.7% grade 2; 26.0% grade 3; 3.9% grade 4), sensory neuropathy (28.3% grade 1; 14.5% grade 2; 13.4% grade 3), tinnitus (25.0% grade 1; 7.1% grade 2; 7.5% grade 3), and hearing damage (24.5% grade 1; 13.5% grade 2; 1.2% grade 3) **(Table 2**). Raynaud phenomenon occurred in approximately 33% of TCS (15.6% grade 1, 8.7% grade 2, 9.1% grade 3), and pain in about 25% (13.6% grade 1, 9.8% grade 2, and 1.5% grade 3). Hypogonadism (10.2% grade 2) and erectile dysfunction (15.9% grade 1, 12.5% grade 2) were also observed.

Figure 1 depicts the CBM score. Approximately 20% TCS had a score of high (N=180; 14.8%), very high (N=46; 3.8%) or severe (N=1; 0.1%), whereas 76% had a score of very low, low, or medium (N=104; 8.6%, N=458; 37.7% and N=360; 29.7%, respectively). Only 5.4% of TCS had no AHOs. All 47 participants with a very high or severe score had grade 4 obesity.

Bivariate associations of clinical, sociodemographic, and health behavior factors with CBM score are shown in **Supplemental Table 3**. In a multivariable model (**Table 3**) controlling for time since chemotherapy and enrollment center, the following were significantly associated with higher CBM score: older attained age (OR=1.18 per 5 years), BEPX4 (OR=1.44 versus BEPX3), VIPX4 (OR=1.96 versus BEPX3), below college-level education (OR=1.44), current disability leave (OR=3.53), and former or current smoking status (OR=1.28). Although the OR for VIPX4 was slightly higher than that

for BEPX4, the difference was not significant (p=0.36). Disease stage was not associated with CBM score (p=0.48), suggesting that increased scores after BEPX4 or VIPX4 were not explained by more advanced tumor status. CBM scores after EPX4 and BEPX3 were similar (p=0.65). No significant differences were observed for individual AHOs except Raynaud phenomenon (P<0.001), for which prevalence and severity after BEPX3 (n=183 patients (39.8%): 18.5% grade 1, 10.4% grade 2, and 10.9% grade 3) exceeded EPX4 (n=84 patients (23.8%): 12.2% grade 1, 16.8% grade 2, and 4.8% grade 3).

Asian race (OR=0.41) and vigorous exercise (OR=0.68) were inversely associated with higher CBM score. Lower risk in Asian TCS reflects the fact that fewer patients had higher severity grades for 15 of 22 AHOs vs. whites (e.g., peripheral sensory neuropathy: grade 3 [8.5% vs. 13.5%]; hearing loss: grade 2 [8.5% vs. 14.1%], grade 3 [0% vs. 1.2%]). Similar trends were observed for autonomic neuropathy, tinnitus, Raynaud phenomenon, pain, kidney disease, hypertension, CAD, peripheral artery disease, obesity, thyroid disease, depression/anxiety, erectile dysfunction, and hypogonadism.

The relationship between cumulative cisplatin dose and overall CBM score was of borderline significance (OR per 100 mg/m^2=1.16; 95%CI 0.99-1.37; p=0.064) in the multivariable model. However, when limited to conditions previously attributed to cisplatin,[14,15] each 100 mg/m^2 increase in cumulative dose was associated with significantly worse CBM_{Pt} (OR per 100mg/m^2=1.34; 95%CI, 1.14-1.58; p<0.001).

Increasing CBM score was significantly associated with worse self-reported health. Compared to patients with a score of none, the risk of worse self-reported health among those scored as very low, low, medium, high, or very high/severe was 1.94 (95%CI 1.08-3.48), 2.82 (95%CI 1.72-4.62), 5.91 (95%CI 3.56-9.81), 10.90 (95%CI 6.28-18.93), and 34.17 (95%CI 16.54-70.62), respectively.

Results from both variable-clustering methods converged in the analysis of AHOs to yield six major groups of signs/symptoms (chi-square for model fit: P<0.001) with pairwise ORs for given clusters as follows: (1) hearing loss/damage, tinnitus (OR=16.3); (2) metabolic disorders (diabetes, hypertension, hyperlipidemia) (OR=9.8); (3) neuropathy and related conditions (sensory neuropathy,

autonomic neuropathy, pain, Raynaud phenomenon) (OR=5.5); (4) cardiovascular disease (CVD) and related conditions (CAD, stroke, kidney disease, peripheral artery disease, thromboembolism, and obesity) (OR=5.0); (5) erectile dysfunction (ED) and thyroid disease (OR=4.2); and (6) hypogonadism and depression/anxiety (OR=2.8). Clusters (1) and (3), although distinct, were strongly correlated ($r=0.658$; $p<0.001$), as were clusters (5) and (6) ($r=0.914$; $p<0.001$).

Discussion

Our results are based on the largest study to date of TCS given contemporary cisplatin-based chemotherapy. For the first time, to our knowledge, we characterize the CBM, showing that even at a young age almost one in five patients had a score of high to severe, with only 5% reporting no AHOs. Although CBM was higher in TCS given BEPX4 or VIPX4 (vs. BEPX3), scores did not differ significantly between these two regimens ($p=0.36$). Neither did CBM differ between BEPX3 and EPX4, the standard approaches for good risk disease. The higher prevalence and severity of Raynaud phenomenon after BEPX3 is consistent with the known relationship with bleomycin,[7] although it may also be related to cisplatin.[19] Increasing cumulative cisplatin dose significantly increased risk for a higher CBM score for AHOs related to neuropathy, ototoxicity and kidney disease. The strong association between higher CBM score and worse self-reported health indicates that the score reflects a health status perceptible to patients. These and other new findings are discussed below.

Previous U.S. investigations of TCS[2,20-24] have been limited in scope, generally either not addressing AHOs[21,23,24] or evaluating less than five conditions[22] (**Supplemental Table 4).** Although three studies obtained treatment information from medical records, only Oh et al.[22] (N=143 patients) examined AHOs (n=4) by therapy. Hashibe et al.[20] evaluated AHOs through linkage with ICD-9 codes, but results were not presented by treatment, and only 168 patients received chemotherapy (type unspecified). In contrast, we evaluated a wide spectrum of AHOs by type and severity among >1,200 TCS with detailed treatment information. The resultant CBM score comprises a range of AHOs likely related to TC and its treatment, and also to long-term platinum retention. After chemotherapy

completion, circulating serum platinum remains measurable at levels up to 1,000 times above normal for 20 years.[25] Ongoing endothelial cell and vascular damage[26] occur for many years, and long-term serum platinum levels have been significantly related to neuropathy,[27] hypertension,[28] and hypercholesterolemia.[28]

Since TC occurs largely in white males,[29] data on Asian patients are sparse. Decreased risks of a higher CBM score in Asian vs. white TCS largely reflected the lower occurrence of high severity grades in Asians for most AHOs. These included known treatment-related toxicities, possibly reflecting differences in drug absorption, distribution, metabolism and excretion, but also others. Although we adjusted for sociodemographic and health behavior factors, it is possible that other unmeasured influences may have accounted for this finding, which remains to be confirmed.

It is noteworthy that although the CBM score was slightly higher after VIPX4 than after BEPX4, the difference was not significant (p=0.36). Both are standard chemotherapy for intermediate and poor-risk disease,[5,6] showing equivalent survival. Although an early, randomized trial showed that VIPX4 was associated with greater acute toxicity than BEPX4,[30] no study has subsequently addressed long-term AHOs, as done here. Additional follow-up, as planned for this unique cohort, will be required to further quantify the CBM associated with each regimen. CBM was also similar for BEPX3 vs. EPX4, the two commonly applied regimens for good-risk disease. In a curable disease such as TC with long life expectancy and equivalent therapy options, the availability of AHO data becomes increasingly important to inform treatment decisions.[8]

The striking association between CBM score and self-reported health indicates that the score captures outcomes that impact patients' self-perception of health. The risk of worse self-reported health among patients with very high/severe CBM scores rose to over 30-fold compared to those with a score of none. These results further underscore the need to assess outcomes that impact self-perceived health, as these can guide the development of survivorship care strategies that are valued by patients.

To our knowledge, this is the first variable-based factor analysis of AHOs in long-term cancer survivors. Prior analyses have largely been conducted in patients either during cancer treatment,[31,32]

shortly after therapy completion,[33,34] or during palliative/hospice care.[35] Only Kim et al.[36] evaluated patients who were either 2-5 years (N=66) or >5 years (N=56) post-cancer diagnosis, although some were still undergoing treatment. Factor analysis provides insights into groups of conditions that may co-occur and perhaps share etiology. For example, hearing loss and tinnitus reflect known cisplatin-associated damage to the auditory system.[10,37] Associations between neuropathy and Raynaud's phenomenon have been reported in non-chemotherapy exposed individuals,[38,39] although the biologic basis is incompletely understood and co-occurrence could reflect symptom cross-reporting. Pain is frequently associated with chemotherapy-induced peripheral neuropathy, with no agents currently available for prevention or treatment.[40]

The cluster of hyperlipidemia, hypertension, and diabetes present at time of clinical evaluation represents components of the metabolic syndrome (MetS),[41] consistent with studies reporting increased MetS risk among European TCS.[42-45] The co-occurrence of AHOs related to CVD supports European investigations that show a 1.4-to-7-fold higher CVD risk among cisplatin-treated TCS vs. either the general population or patients managed with surgery alone.[26,46-49] Presentation with one or more of these AHOs suggests closer screening for other cluster-related conditions that could signal elevated risk for CVD morbidity and mortality.[7] Hypogonadism and depression, respectively, represent a biologic consequence of TC treatment[50,51] and possible associated psychological outcome. A potential relationship between hypogonadism and depression in the general population has been recognized, with other symptoms including muscle weakness and loss of energy.[52-56]

An association of ED and thyroid disease has not been previously shown in TCS, as it has in non-cancer populations.[57-63] Of 39 TCS with thyroid disease, 33 and 6 reported hypothyroidism and hyperthyroidism, respectively. Although associations of hypothyroidism[57,62,63] and hyperthyroidism[57,61-63] with ED were observed in several studies in non-cancer populations, a relationship with hypothyroidism was not confirmed in the largest investigation to date,[61] possibly due to the low prevalence, and requires further investigation.

The strong association between vigorous physical activity and lower CBM score, as well as with a reduced absolute number of AHOs in prior analyses,[2] can inform future intervention strategies. Studies of childhood cancer survivors have shown that exercise reduces the risk of late effects such as CVD,[64] and the same likely applies to TCS. The apparent inverse relation between increased risk of a high CBM score and follow-up time is due to the disproportionate contribution of early-onset toxicities (e.g., neuropathy, tinnitus), which are more prevalent than later-onset toxicities (e.g., hypercholesterolemia, hypertension), reflecting the relatively short median follow-up time and young cohort age.

A major strength of this study is the estimation of both the number and severity of AHOs in the largest TCS cohort to date treated primarily with EPX4, BEPX3, BEPX4 or VIPX4. Other strengths include the high participation rate (93%), detailed medical chart abstraction, and estimation of risk without the confounding effect of radiotherapy. An inherent limitation to all cross-sectional studies is the inability to assess causality between clinical, sociodemographic and health behavior characteristics and CBM score. AHOs were largely self-reported without baseline data, similar to previous TCS studies.[21,23,65] As in Geenen et al.,[15] a limitation is that we could not compare the CBM score to that of a normative population, given the unavailability of data. Equivalent weight was assigned to all AHOs, whereas TCS may weigh these differently; some AHOs capture symptoms that can markedly affect TCS (e.g. neuropathy) whereas others encompass conditions treated by medications that may be less bothersome (e.g. hypertension). Further studies are needed to investigate the impact of specific AHOs on health-related quality of life in this under-studied population.

In conclusion, at a median follow-up of only 4.2 years, almost 1 in 5 TCS have a CBM score of high, very high, or severe. Importantly, no difference in CBM score was observed among TCS receiving BEPX4 vs. VIPX4, or among those given EPX4 vs. BEPX3, although it will be important to monitor patients long-term. The value of variable-clustering analysis in revealing the co-occurrence of AHOs is underscored by our findings, and should be considered for other groups of long-term cancer survivors to highlight potential areas of research into mechanistic bases of toxicities. Ongoing genetic research in

our cohort has already begun to characterize biologic pathways underlying cisplatin-related toxicities[66,67] and can identify new research opportunities aimed at developing agents to prevent, mitigate and treat adverse sequelae, not only among TCS, but other survivors after cisplatin-based chemotherapy. In the interim, if confirmed, our results could inform survivorship care strategies and assist health care providers in identifying conditions, or groups of conditions, for which to screen, counsel, and treat TCS.

Acknowledgments:

Members of the Platinum Study Group include: Howard D. Sesso (Brigham and Women's Hospital); Clair J. Beard and Stephanie Curreri (Dana-Farber Cancer Institute); Lois B. Travis, Lawrence H. Einhorn, Mary Jacqueline Brames, and Kelli Norton (Indiana University); Darren R. Feldman, Erin Jacobsen, and Deborah Silber (Memorial Sloan Kettering Cancer Center); Rob Hamilton and Lynn Anson-Cartwright (Princess Margaret Hospital); Nancy J. Cox and M. Eileen Dolan (University of Chicago); Robert Huddart (Royal Marsden Hospital); David J. Vaughn, Linda Jacobs, Sarah Lena Panzer, and Donna Pucci (University of Pennsylvania); Debbie Baker, Cindy Casaceli, Chunkit Fung, Eileen Johnson, and Deepak Sahasrabudhe (University of Rochester); and Robert D. Frisina (University of South Florida). The Platinum Study Group Advisory Committee consists of George Bosl (Memorial Sloan Kettering Cancer Center), Sophie D. Fossa (Norwegian Radium Hospital), Mary Gospodarowicz (Princess Margaret Hospital), Leslie L. Robison (St. Jude Children's Research Hospital), and Steven E. Lipshultz (Wayne State University).

References

1. de Moor JS, Mariotto AB, Parry C, et al: Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev 22:561-70, 2013

2. Fung C, Sesso HD, Williams AM, et al: Multi-Institutional Assessment of Adverse Health Outcomes Among North American Testicular Cancer Survivors After Modern Cisplatin-Based Chemotherapy. J Clin Oncol 35:1211-1222, 2017

3. Einhorn LH, Donohue J: Cis-diamminedichloroplatinum, vinblastine, and bleomycin combination chemotherapy in disseminated testicular cancer. Ann Intern Med 87:293-8, 1977

4. Miller KD, Siegel RL, Lin CC, et al: Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 66:271-89, 2016

5. Hanna N, Einhorn LH: Testicular cancer: a reflection on 50 years of discovery. J Clin Oncol 32:3085-92, 2014

6. Hanna NH, Einhorn LH: Testicular cancer--discoveries and updates. N Engl J Med 371:2005-16, 2014

7. Glendenning JL, Barbachano Y, Norman AR, et al: Long-term neurologic and peripheral vascular toxicity after chemotherapy treatment of testicular cancer. Cancer 116:2322-31, 2010

8. Oldenburg J, Gietema JA: The Sound of Silence: A Proxy for Platinum Toxicity. J Clin Oncol 34:2687-9, 2016

9. Travis LB, Fossa SD, Sesso HD, et al: Chemotherapy-induced peripheral neurotoxicity and ototoxicity: new paradigms for translational genomics. J Natl Cancer Inst 106, 2014

10. Frisina RD, Wheeler HE, Fossa SD, et al: Comprehensive Audiometric Analysis of Hearing Impairment and Tinnitus After Cisplatin-Based Chemotherapy in Survivors of Adult-Onset Cancer. J Clin Oncol, 2016

11. Chasan-Taber S, Rimm EB, Stampfer MJ, et al: Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. Epidemiology 7:81-6, 1996

12. Taylor HL, Jacobs DR, Jr., Schucker B, et al: A questionnaire for the assessment of leisure time physical activities. J Chronic Dis 31:741-55, 1978

13. Ainsworth BE, Haskell WL, Herrmann SD, et al: 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 43:1575-81, 2011

14. National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0, NIH publication # 09-7473, NCI, NIH, DHHS. May 29, 2009

15. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al: Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 297:2705-15, 2007

16. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572-82, 2006

17. Haugnes HS, Bosl GJ, Boer H, et al: Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. J Clin Oncol 30:3752-63, 2012

18. Travis LB, Beard C, Allan JM, et al: Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst 102:1114-30, 2010

19. Brydoy M, Oldenburg J, Klepp O, et al: Observational study of prevalence of long-term Raynaud-like phenomena and neurological side effects in testicular cancer survivors. J Natl Cancer Inst 101:1682-95, 2009

20. Hashibe M, Abdelaziz S, Al-Temimi M, et al: Long-term health effects among testicular cancer survivors. J Cancer Surviv 10:1051-1057, 2016

21. Kim C, McGlynn KA, McCorkle R, et al: Quality of life among testicular cancer survivors: a case-control study in the United States. Qual Life Res 20:1629-37, 2011

22. Oh JH, Baum DD, Pham S, et al: Long-term complications of platinum-based chemotherapy in testicular cancer survivors. Med Oncol 24:175-81, 2007

23. Reilley MJ, Jacobs LA, Vaughn DJ, et al: Health behaviors among testicular cancer survivors. J Community Support Oncol 12:121-8, 2014

24. Shinn EH, Basen-Engquist K, Thornton B, et al: Health behaviors and depressive symptoms in testicular cancer survivors. Urology 69:748-53, 2007

25. Gerl A, Schierl R: Urinary excretion of platinum in chemotherapy-treated long-term survivors of testicular cancer. Acta Oncol 39:519-22, 2000

26. Feldman DR, Schaffer WL, Steingart RM: Late cardiovascular toxicity following chemotherapy for germ cell tumors. J Natl Compr Canc Netw 10:537-44, 2012

27. Sprauten M, Darrah TH, Peterson DR, et al: Impact of long-term serum platinum concentrations on neuro- and ototoxicity in Cisplatin-treated survivors of testicular cancer. J Clin Oncol 30:300-7, 2012

28. Boer H, Proost JH, Nuver J, et al: Long-term exposure to circulating platinum is associated with late effects of treatment in testicular cancer survivors. Ann Oncol 26:2305-10, 2015

29. Ghazarian AA, Trabert B, Devesa SS, et al: Recent trends in the incidence of testicular germ cell tumors in the United States. Andrology 3:13-8, 2015

30. Nichols CR, Catalano PJ, Crawford ED, et al: Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: an Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B Study. J Clin Oncol 16:1287-93, 1998

31. Baggott C, Cooper BA, Marina N, et al: Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy. Cancer Nurs 35:19-28, 2012

32. Huang J, Gu L, Zhang L, et al: Symptom Clusters in Ovarian Cancer Patients With Chemotherapy After Surgery: A Longitudinal Survey. Cancer Nurs 39:106-16, 2016

33. Kenne Sarenmalm E, Browall M, Gaston-Johansson F: Symptom burden clusters: a challenge for targeted symptom management. A longitudinal study examining symptom burden clusters in breast cancer. J Pain Symptom Manage 47:731-41, 2014

34. Skerman HM, Yates PM, Battistutta D: Cancer-related symptom clusters for symptom management in outpatients after commencing adjuvant chemotherapy, at 6 months, and 12 months. Support Care Cancer 20:95-105, 2012

35. Stapleton SJ, Holden J, Epstein J, et al: Symptom clusters in patients with cancer in the hospice/palliative care setting. Support Care Cancer 24:3863-71, 2016

36. Kim M, Kim K, Lim C, et al: Symptom Clusters and Quality of Life According to the Survivorship Stage in Ovarian Cancer Survivors. West J Nurs Res:193945917701688, 2017

37. Bauer CA, Brozoski TJ: Cochlear structure and function after round window application of ototoxins. Hear Res 201:121-31, 2005

38. Koszewicz M, Gosk-Bierska I, Jerzy G, et al: Peripheral nerve changes assessed by conduction velocity distribution in patients with primary Raynaud's phenomenon and dysautonomia. Int Angiol 30:375-9, 2011

39. Manek NJ, Holmgren AR, Sandroni P, et al: Primary Raynaud phenomenon and small-fiber neuropathy: is there a connection? A pilot neurophysiologic study. Rheumatol Int 31:577-85, 2011

40. Hershman DL, Lacchetti C, Dworkin RH, et al: Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 32:1941-67, 2014

41. Alberti KG, Eckel RH, Grundy SM, et al: Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120:1640-5, 2009

42. Haugnes HS, Aass N, Fossa SD, et al: Components of the metabolic syndrome in long-term survivors of testicular cancer. Ann Oncol 18:241-8, 2007

43. de Haas EC, Altena R, Boezen HM, et al: Early development of the metabolic syndrome after chemotherapy for testicular cancer. Ann Oncol 24:749-55, 2013

44. Wethal T, Kjekshus J, Roislien J, et al: Treatment-related differences in cardiovascular risk factors in long-term survivors of testicular cancer. J Cancer Surviv 1:8-16, 2007

45. Willemse PM, Burggraaf J, Hamdy NA, et al: Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. Br J Cancer 109:60-7, 2013

46. Haugnes HS, Wethal T, Aass N, et al: Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. J Clin Oncol 28:4649-57, 2010

47. Huddart RA, Norman A, Shahidi M, et al: Cardiovascular disease as a long-term complication of treatment for testicular cancer. J Clin Oncol 21:1513-23, 2003

48. Meinardi MT, Gietema JA, van der Graaf WT, et al: Cardiovascular morbidity in long-term survivors of metastatic testicular cancer. J Clin Oncol 18:1725-32, 2000

49. van den Belt-Dusebout AW, Nuver J, de Wit R, et al: Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 24:467-75, 2006

50. Bandak M, Jorgensen N, Juul A, et al: Testosterone deficiency in testicular cancer survivors - a systematic review and meta-analysis. Andrology 4:382-8, 2016

51. Sprauten M, Brydoy M, Haugnes HS, et al: Longitudinal serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels in a population-based sample of long-term testicular cancer survivors. J Clin Oncol 32:571-8, 2014

52. Amiaz R, Seidman SN: Testosterone and depression in men. Curr Opin Endocrinol Diabetes Obes 15:278-83, 2008

53. Eberhard J, Stahl O, Cohn-Cedermark G, et al: Emotional disorders in testicular cancer survivors in relation to hypogonadism, androgen receptor polymorphism and treatment modality. J Affect Disord 122:260-6, 2010

54. Gunn ME, Lahteenmaki PM, Puukko-Viertomies LR, et al: Potential gonadotoxicity of treatment in relation to quality of life and mental well-being of male survivors of childhood acute lymphoblastic leukemia. J Cancer Surviv 7:404-12, 2013

55. Hintikka J, Niskanen L, Koivumaa-Honkanen H, et al: Hypogonadism, decreased sexual desire, and long-term depression in middle-aged men. J Sex Med 6:2049-57, 2009

56. Johnson JM, Nachtigall LB, Stern TA: The effect of testosterone levels on mood in men: a review. Psychosomatics 54:509-14, 2013

57. Carani C, Isidori AM, Granata A, et al: Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. J Clin Endocrinol Metab 90:6472-9, 2005

58. Keller J, Chen YK, Lin HC: Hyperthyroidism and erectile dysfunction: a population-based case-control study. Int J Impot Res 24:242-6, 2012

59. Corona G, Isidori AM, Aversa A, et al: Endocrinologic Control of Men's Sexual Desire and Arousal/Erection. J Sex Med 13:317-37, 2016

60. Maggi M, Buvat J, Corona G, et al: Hormonal causes of male sexual dysfunctions and their management (hyperprolactinemia, thyroid disorders, GH disorders, and DHEA). J Sex Med 10:661-77, 2013

61. Corona G, Wu FC, Forti G, et al: Thyroid hormones and male sexual function. Int J Androl 35:668-79, 2012

62. Veronelli A, Masu A, Ranieri R, et al: Prevalence of erectile dysfunction in thyroid disorders: comparison with control subjects and with obese and diabetic patients. Int J Impot Res 18:111-4, 2006

63. Krassas GE, Tziomalos K, Papadopoulou F, et al: Erectile dysfunction in patients with hyper- and hypothyroidism: how common and should we treat? J Clin Endocrinol Metab 93:1815-9, 2008

64. Jones LW, Liu Q, Armstrong GT, et al: Exercise and risk of major cardiovascular events in adult survivors of childhood hodgkin lymphoma: a report from the childhood cancer survivor study. J Clin Oncol 32:3643-50, 2014

65. Dahl CF, Haugnes HS, Bremnes R, et al: A controlled study of risk factors for disease and current problems in long-term testicular cancer survivors. J Cancer Surviv 4:256-65, 2010

66. Dolan ME, El Charif O, Wheeler HE, et al: Clinical and Genome-Wide Analysis of Cisplatin-Induced Peripheral Neuropathy in Survivors of Adult-Onset Cancer. Clin Cancer Res, 2017

67. Wheeler HE, Gamazon ER, Frisina RD, et al: Variants in WFS1 and Other Mendelian Deafness Genes Are Associated with Cisplatin-Associated Ototoxicity. Clin Cancer Res 23:3325-3333, 2017

68. Postma TJ, Aaronson NK, Heimans JJ, et al: The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. Eur J Cancer 41:1135-9, 2005

69. Oldenburg J, Fossa SD, Dahl AA: Scale for chemotherapy-induced long-term neurotoxicity (SCIN): psychometrics, validation, and findings in a large sample of testicular cancer survivors. Qual Life Res 15:791-800, 2006

70. Ventry IM, Weinstein BE: The hearing handicap inventory for the elderly: a new tool. Ear Hear 3:128-34, 1982

71. Ware JE, Jr., Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473-83, 1992

Table 1. Clinical, Sociodemographic and Health Behavior Characteristics of 1,214 Survivors of Cisplatin-Treated Germ Cell Tumors (GCT)

Clinical Characteristic, number (%)	
Age at GCT diagnosis, years[a]	
Median [range]	30 [15 - 60]
< 20	89 (7.3)
20 to 29	482 (39.7)
30 to 39	403 (33.2)
≥ 40	232 (19.2)
Age at evaluation, years	
Median [range]	37 [18 - 74]
<20	9 (0.7)
20 to 29	265 (21.8)
30 to 39	436 (35.9)
40 to 49	314 (25.9)
50 to 59	164 (13.5)
60 to 69	26 (2.1)
Calendar year of diagnosis[b]	
Before 2000	146 (12.0)
2000-2004	145 (11.9)
2005-2009	317 (26.1)
2010-2016	598 (49.3)
Histological type of GCT	
Seminoma	310 (25.5)
Non-seminoma	885 (72.9)
GCT, NOS	19 (1.6)
GCT site[c]	
Testis	1069 (88.1)
Extragonadal	135 (11.1)
Type of cisplatin-based chemotherapy[d]	
BEP	710 (58.5)
≤ 2 cycles	21
3 cycles	460
4 cycles	222
≥ 5 cycles	7
EP	388 (32.0)
≤ 3 cycles	23
4 cycles	353
≥ 5 cycles	12
VIP	44 (3.6)
3 cycles	4
4 cycles	32
≥ 5 cycles	8
Other[e]	69 (5.7)
≤ 2 cycles	11
3 cycles	8
4 cycles	41
≥ 5 cycles	9

Cumulative dose of cisplatin (mg/m^2)[f]	
Median [range]	400 [100 - 828]
< 300	61 (4.9)
300	447 (36.8)
301-399	44 (3.2)
400	589 (48.5)
> 400	55 (4.4)
Clinical Characteristic, number (%)	
Retroperitoneal lymph node dissection (RPLND)[g]	
Yes	562 (46.3)
No	639 (52.6)
Time since completion of chemotherapy (years)[h]	
Median [range]	4.2 [1 - 30]
< 2	329 (27.1)
2 to 5	423 (34.8)
6 to 9	186 (15.3)
≥ 10	261 (21.5)
Sociodemographic characteristic, number (%)	
Race[i]	
White	1,036 (85.3)
African American	16 (1.3)
Asian	59 (4.9)
Other	68 (5.6)
Marital status[j]	
Single or never married	389 (32.0)
Married/living as married	740 (61.0)
Widowed/divorced/separated	70 (5.8)
Education[k]	
High school or less	139 (11.5)
After high school but not college graduate	289 (23.8)
College or university graduate	508 (41.9)
Post-graduate	275 (22.7)
Current employment status[l]	
Unemployed	74 (6.1)
Employed	1,077 (88.7)
Retired	15 (1.2)
On disability leave	30 (2.5)
Health behavior, number (%)	
Smoking status[m]	
Never	714 (58.8)
Former	392 (32.3)
Current	107 (8.8)
Average number of alcoholic drinks in past year[n]	
Rarely or never	239 (19.7)
1 to 3 per month	180 (14.8)
1 to 6 per week	569 (46.9)
≥ 1 daily	218 (18.0)
Engage in vigorous physical activity (≥6 METs)[o]	
Yes	835 (68.8)
No	378 (31.1)

Abbreviations: BEP, bleomycin, etoposide, cisplatin; EP, etoposide, cisplatin; GCT, germ cell tumor; MET, metabolic equivalent task; NOS, not otherwise specified; RPLND, retroperitoneal lymph node dissection; VIP, etoposide, ifosfamide, cisplatin.

[a] Age at diagnosis was not available for 8 individuals.
[b] Year of GCT diagnosis was not available for 8 individuals.
[c] GCT site was not available for 10 individuals.
[d] Of the 52 patients given VIPX4, 44% had mediastinal disease whereas 47% had disease confined to the testis, and in the remainder (9%), other extra-gonadal sites were involved. This is in contrast to the smaller percentage of patients with mediastinal disease (i.e. 7.2% or less) in the other treatment groups.
[e] Other chemotherapy regimens included cisplatin and ifosfamide (N=25); cisplatin, vinblastine, and bleomycin (N=6); ifosfamide, bleomycin, cisplatin, and etoposide (N=6); and other cisplatin-based regimens (N=32). Number of cycles was not available for 4 individuals who received a chemotherapy regimen designated 'Other'.
[f] Cumulative dose of cisplatin was not available for 18 individuals.
[g] RPLND status was not available for 13 individuals.
[h] Time since completion of chemotherapy was not available for 15 individuals.
[i] Race was not stated for 19 individuals.
[j] Marital status was not stated for 15 individuals.
[k] Education status was not stated for 3 individuals.
[l] Employment status was not stated for 18 individuals.
[m] Smoking status was not stated for 1 individual.
[n] Alcohol consumption was not stated for 8 individuals.
[o] Exercise was assessed in this study using a validated questionnaire[11,12] that asks participants to report their average time per week (over the past year) spent at each of nine recreational activities: walking or hiking (including walking to work); jogging (slower than 10 minute miles); running (10 minute miles or faster); bicycling (including stationary bike); aerobic exercise or dance/exercise machines; lower intensity exercise/yoga/stretching/toning; tennis, squash or racquetball; lap swimming; and weight lifting/strength training. Each physical activity was assigned a metabolic equivalent (MET) value. MET values are a commonly used metric for describing the relative energy expenditure of a specific type of physical activity (1 MET=1 kcal/kg/hour, or the energy cost of sitting quietly). The MET values for each activity were then used to calculate MET-hours/week for each participant, and these were grouped into categories of vigorous or non-vigorous physical activity following standard definitions.[13] Physical activity was not stated for 1 individual.

Table 2. Prevalence of Adverse Health Outcome (AHO) By Severity Grade, N (%)

	AHO: all grades	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral sensory neuropathy[a]	683 (56.3)	344 (28.3)	176 (14.5)	163 (13.4)	NA[b]
Autonomic neuropathy[c,d]	323 (26.6)	234 (19.3)	68 (5.6)	21 (1.7)	NA
Hearing damage[c]	476 (39.2)	297 (24.5)	164 (13.5)	15 (1.2)	0
Tinnitus[c]	481 (39.6)	304 (25.0)	86 (7.1)	91 (7.5)	NA
Raynaud phenomenon[c]	405 (33.4)	189 (15.6)	105 (8.7)	111 (9.1)	NA
Pain[a]	302 (24.9)	165 (13.6)	119 (9.8)	18 (1.5)	NA
Kidney disease[a]	30 (2.5)	27 (2.2)	3 (0.3)	NA	NA
Hypercholesterolemia[a]	96 (7.9)	NA	96 (7.9)	NA	NA
Hypertriglyceridemia[a]	6 (0.5)	NA	6 (0.5)	NA	NA
Hypertension[a]	114 (9.4)	NA	114 (9.4)	NA	NA
Diabetes[a]	37 (3.0)	NA	20 (1.7)	17 (1.4)	NA
Coronary artery disease[a]	20 (1.6)	4 (0.3)	7 (0.6)	9 (0.7)	NA
Transient ischemic attack[c]	8 (0.7)	8 (0.7)	NA	NA	NA
Stroke[c]	6 (0.5)	NA	6 (0.5)	NA	0
Peripheral artery disease[a]	56 (4.6)	27 (2.2)	14 (1.2)	15 (1.2)	NA
Thromboembolic event[a]	88 (7.2)	NA	44 (3.6)	44 (3.6)	NA
Obesity[e]	868 (71.5)	NA[f]	506 (41.7)	315 (26.0)	47 (3.9)
Thyroid disease[a]	39 (3.2)	20 (1.7)	19 (1.6)	NA	NA
Anxiety and/or depression[g]	75 (6.2)	NA	75 (6.2)	NA	NA
Erectile dysfunction[a]	345 (28.4)	193 (15.9)	152 (12.5)	NA	NA
Hypogonadism[g]	124 (10.2)	NA	124 (10.2)	NA	NA

[a] Based on patient reported outcomes and prescription medication use.
[b] NA, not applicable, as data needed to assign these toxicities according to the CTCAE definitions were not captured in the present study.
[c] Based on patient reported outcomes
[d] Among participants with grade 0, grade 1, grade 2, and grade 3 autonomic neuropathy, 22, 7, 2, and 1, respectively, reported taking a beta-blocker.
[e] Calculated using weight and height assessments from physical exam conducted at clinical evaluation.
[f] CTCAE does not include a grade 1 for obesity
[g] Based on prescription medication use.

Table 3. Multivariable Ordinal Logistic Regression[a] of Factors Associated With CBM Score

	Odds Ratio (95% CI)	p-value
Age at evaluation (per 5 years)[b]	1.18 (1.10, 1.26)	**<0.001**
Time since chemotherapy completion, years		
< 2	Ref.	-
2-5	0.91 (0.68, 1.23)	0.54
6-9	0.61 (0.42, 0.89)	**0.010**
10+	0.55 (0.38, 0.85)	**0.002**
Race		
White	Ref.	-
Black/African-American	1.56 (0.49, 5.03)	0.45
Asian	0.41 (0.23, 0.72)	**0.002**
Other	1.05 (0.63, 1.76)	0.84
Education		
College or post-college graduate	Ref.	-
Less than college education	1.44 (1.11, 1.87)	**0.006**
Current employment status		
Employed	Ref.	-
Unemployed	0.90 (0.55, 1.47)	0.66
Retired	1.10 (0.36, 3.39)	0.87
On disability leave	3.53 (1.57, 7.95)	**0.002**
Smoking status		
Never	Ref.	-
Current or Former	1.28 (1.02, 1.63)	0.037
Vigorous physical activity (≥6 METs)[c]		
No	Ref.	-
Yes	0.68 (0.52, 0.89)	**0.004**
RPLND[d]		
No	Ref.	-
Yes	0.88 (0.69, 1.12)	0.31
Type of chemotherapy[e]		
BEPX3	Ref.	-
EPX4	1.09 (0.75, 1.60)	0.65
BEPX4	1.44 (1.04, 1.98)	**0.028**
VIPX4	1.96 (1.04, 3.71)	**0.039**

Abbreviations: BEP, bleomycin, etoposide, cisplatin; EP, etoposide, cisplatin; MET, metabolic equivalent task; RPLND, retroperitoneal lymph node dissection; VIP, etoposide, ifosfamide, cisplatin

[a] Odds ratios and p-values are from an adjusted model that includes all other variables listed in the table, as well as enrollment center, with CBM score as the outcome (dependent) variable. The 'very high' and 'severe' categories were collapsed due to sparse data. Analysis includes 1,013 (83.4%) testicular cancer survivors with non-missing data for all variables in the model.

[b] Age at diagnosis was not included in the model given the strong correlation with age at evaluation (r=0.81), which was included

[c] See Table 1, footnote o and Appendix-Supplemental Methods for details on assessment of physical activity.

[d] RPLND was retained in the multivariable model to control for potential residual confounding, given its correlation with chemotherapy regimen (P < 0.001); approximately 34%, 55%, 66%, and 44% of TCS treated with BEPX3, EPX4, BEPX4, and VIPX4, respectively, had an RPLND.

[e] Disease stage was not significantly associated with CBM score (P = 0.48) , suggesting that increased scores after BEPX4 or VIPX4 were not explained by more advanced tumor status

Figure 1. Distribution of Cumulative Burden of Morbidity (CBM) Score Among 1,214 Participants in the Platinum Study.