JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 3, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2015.06.028

Valvular Dysfunction in Lymphoma Survivors Treated With Autologous Stem Cell Transplantation

A National Cross-Sectional Study

Klaus Murbraech, MD,[a] Torgeir Wethal, MD, PhD,[b] Knut B. Smeland, MD,[c,d] Harald Holte, MD, PhD,[d] Jon Håvard Loge, MD, PhD,[e,f] Espen Holte, MD,[b] Assami Rösner, MD, PhD,[g] Håvard Dalen, MD, PhD,[h,i] Cecilie E. Kiserud, MD, PhD,[c,d] Svend Aakhus, MD, PhD[a,j]

ABSTRACT

OBJECTIVES This study assessed the prevalence and associated risk factors for valvular dysfunction (VD) observed in adult lymphoma survivors (LS) after autologous hematopoietic stem cell transplantation (auto-HCT), and to determine whether anthracycline-containing chemotherapy (ACCT) alone in these patients is associated with VD.

BACKGROUND The prevalence of and risk factors for VD in LS after auto-HCT is unknown. Anthracyclines may induce heart failure, but any association with VD is not well-defined.

METHODS This national cross-sectional study included all adult LS receiving auto-HCT from 1987 to 2008 in Norway. VD was defined by echocardiography as either more than mild regurgitation or any stenosis. Observations in LS were compared with a healthy age- and gender-matched (1:1) control group.

RESULTS In total, 274 LS (69% of all eligible) participated. Mean age was 56 ± 12 years, mean follow-up time after lymphoma diagnosis was 13 ± 6 years, and 62% of participants were males. Mean cumulative anthracycline dosage was 316 ± 111 mg/m^2, and 35% had received radiation therapy involving the heart (cardiac-RT). VD was observed in 22.3% of the LS. Severe VD was rare (n = 9; 3.3% of all LS) and mainly aortic stenosis (n = 7). We observed VD in 16.7% of LS treated with ACCT alone (n = 177), corresponding with a 3-fold increased VD risk (odds ratio: 2.9; 95% confidence interval: 1.5 to 5.8; p = 0.002) compared with controls. Furthermore, the presence of aortic valve degeneration was increased in the LS after ACCT alone compared with controls (13.0% vs. 2.9%; p < 0.001). Female sex, age >50 years at lymphoma diagnosis, ≥3 lines of chemotherapy before auto-HCT, and cardiac-RT >30 Gy were identified as independent risk factors for VD in the LS.

CONCLUSIONS In LS, ACCT alone was significantly associated with VD and related to valvular degeneration. Overall, predominantly moderate VD was prevalent in LS, and longer observation time is needed to clarify the clinical significance of this finding. (J Am Coll Cardiol Img 2016;9:230–9) © 2016 by the American College of Cardiology Foundation.

From the [a]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [b]Department of Cardiology, St. Olavs Hospital, University of Trondheim, Trondheim, Norway; [c]National Advisory Unit on Late Effects after Cancer Treatment, Oslo University Hospital, Oslo, Norway; [d]Department of Oncology, Oslo University Hospital, Oslo, Norway; [e]Faculty of Medicine, University of Oslo, Oslo, Norway; [f]Regional Centre for Excellence in Palliative Care, Oslo University Hospital, Oslo, Norway; [g]Department of Cardiology, University Hospital North Norway, Tromsoe, Norway; [h]Department of Medicine, Levanger Hospital, Nord-Trøndelag Health Trust, Levanger, Norway; [i]Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway; and the [j]Faculty of Medicine, University of Trondheim, Trondheim, Norway. The study was supported by South-Eastern Norway Regional Health Authority and Extrastiftelsen, and received no funding from the medical industry. Dr. E. Holte has received honoraria from Actelion Pharmaceuticals Ltd. for lecture, field of pulmonary hypertension. Dr. Dalen has positions at MI Lab, a Centre of Research-based Innovation that is funded by the Research Council of Norway and industry. One of the industry partners is GE Vingmed Ultrasound. The Centre has a total budget of 24 million NOK for the 8-year period from 2007 to 2014, and the contribution from GE Vingmed Ultrasound to this budget is 7 million NOK. GE Vingmed Ultrasound had no role in this manuscript, such as planning of the study, data acquisition, drafting or revision of the manuscript or supply of ultrasound equipment. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 24, 2015; revised manuscript received June 2, 2015, accepted June 4, 2015.

High-dose chemotherapy with auto-logous stem cell transplantation (auto-HCT) has for 30 years been a curative treatment option for patients with relapsed or refractory malignant lymphomas, or as consolidation after first-line therapy in selected patients at particularly high risk for relapse (1–4). Transplantation strategies and supportive care have improved, resulting in increased survival rates (5). Lymphoma survivors (LS) who remain in complete remission for ≥2 years after HCT have favorable long term prognosis, with 10 years survival rates exceeding 80% for certain subgroups (6). Compared with age-matched controls, survivors of HCT (autologous and allogeneic) for hematologic malignancies have a close to 3-fold increased risk of cardiovascular complications (7), and cardiovascular diseases are the leading nonmalignant cause of death (8,9). Consequently, there is an increasing focus on the risk for treatment-related late effects.

SEE PAGE 240

Valvular dysfunction (VD) is a well-known complication after radiation therapy involving the heart (cardiac-RT) (i.e., mediastinal fields and mantle fields) (10,11). The reported prevalence of VD after cardiac-RT for lymphoma varies from 30 to >50% among survivors observed 10 to >20 years after primary treatment (10,12). The development of VD occurs over decades. Our group has previously demonstrated the slow evolving process with fibrosis, valve retraction, and calcification after cardiac-RT, finally causing mainly left-sided regurgitations and stenosis in Hodgkin lymphoma (HL) survivors (13). Other VD-associated risk factors have not been demonstrated consistently, although female sex and additional anthracycline treatment have been identified as aggravating the risk for VD in HL survivors (12,14).

The dose-dependent cardiotoxic potential of anthracyclines (i.e., doxorubicin) is well-documented. Doxorubicin has been reported to induce heart failure in up to 2% and 26% of the treated patients after cumulative doses of 300 and 550 mg/m^2, respectively (15). To the best of our knowledge, data on valvular function in LS after anthracycline exposure without cardiac-RT have not been reported. Hitherto, there are no robust data demonstrating the valvular function in adult LS after auto-HCT, and consequently the prevalence and risk factors for VD in this group of cancer survivors remains unknown.

Consequently, the aims of the present study were first to assess the general prevalence and associated risk factors for VD in adult LS after auto-HCT and second to determine if anthracycline-containing chemotherapy (ACCT) alone was associated with VD in these patients.

MATERIALS AND METHODS

Between March 2012 and March 2014, we performed a cross-sectional, national, multicenter survey in Norway on a broad spectrum of late effects inviting all adult LS treated with auto-HCT (16). Participants fulfilled questionnaires and a comprehensive clinical examination at the hospital where they received their HCT, that is, at 4 sites in Norway (**Figure 1**). The study protocol was endorsed by the Regional Committee for Medical and Health Research Ethics, and written informed consent was given by all participants.

PATIENT POPULATION. Eligibility criteria were treatment with auto-HCT for Hodgkin or non-Hodgkin's lymphoma from 1987, when auto-HCT was first introduced as a treatment option in Norway, until 2008, age ≥18 years at auto-HCT, and alive at time of the survey. The only exclusion criterion was current treatment for relapsed lymphoma. The LS were identified through medical records and registries at each university hospital, and cross-checked against reports from HCT meetings, the clinical quality register for lymphomas at Oslo University Hospital, and radiotherapy registries.

CONTROLS. Controls were drawn from a clinical echocardiographic database consisting of 1,266 participants without diagnosed cardiovascular disease, hypertension, or diabetes mellitus before inclusion, recruited from the third wave of the Nord-Trøndelag Health Study in Norway (17). Controls were matched 1:1 for age, sex, systolic blood pressure, and body mass index.

TREATMENT. Treatment details were obtained retrospectively from medical records, the clinical quality register for lymphomas at the Oslo University Hospital, and radiotherapy registries.

Use of anthracyclines (i.e., doxorubicin and daunorubicin), cyclophosphamide, cisplatinum, and bleomycin were registered and the total cumulative dose calculated for doxorubicin and cyclophosphamide. For daunorubicin, cumulative doses were converted to doxorubicin isotoxic doses using a conventional conversion factor of 0.83 (18). Conditioning regimens consisted of total body irradiation (TBI) and high-dose cyclophosphamide from 1987 to 1995, thereafter of chemotherapy only (carmustine, etoposide, cytarabine, and melphalan [BEAM]). We also

ABBREVIATIONS AND ACRONYMS

ACCT = anthracycline-containing chemotherapy

auto-HCT = autologous hematopoietic stem cell transplantation

cardiac-RT = radiation therapy involving the heart

HL = Hodgkin lymphoma

LS = lymphoma survivor(s)

LV = left ventricle

OR = odds ratio

TBI = total body irradiation

VD = valvular dysfunction