TITLE: Pre-anthracycline left ventricular ejection fraction (LVEF) assessment and long-term cardiovascular (CV) outcomes in adolescent & young adult (AYA) lymphoma survivors.

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INTRODUCTION: Anthracyclines are known to cause long-term cardiotoxicity (Bhakta, 2016; Mulrooney, 2016). Guidelines for post-anthracycline treatment CV risk assessment in AYA patients involve baseline electrocardiogram and follow-up screening with regular echocardiograms (NCCN, 2.2022). Many AYA lymphoma patients are treated as adults, for whom LVEF assessment prior to anthracycline therapy is recommended and routinely performed (Conrad, 2012; Enns, 2018; Peddi, 2019; NCCN 1.2022). Multiple studies have demonstrated LVEF assessment rarely impacts treatment decisions, especially in the absence of CV symptoms or risk factors, adds to unnecessary costs, and delays treatment initiation (Jeyakumar, 2012; Watts, 2012; Truong, 2016; O'Brien, 2019). Our study aimed to determine the pre-treatment LVEF assessment practices in AYA lymphoma patients treated with anthracyclines and its association with long-term cardiotoxicity.

METHODS: Survivors diagnosed with lymphoma >5 years ago and treated with anthracyclines at age 15-39 years were identified in a retrospective single institution registry. To ensure adequate follow-up, at least 2 follow-up visits during 2015-19 were required. Data abstracted on eligible subjects included documentation of pre-treatment LVEF evaluation, clinical rationale, and treatment regimen. CV risk factors and events were collected pre-treatment and during follow-up. Descriptive statistics were used to summarize data.

RESULTS: 64/115 (56%) of AYA lymphoma patients underwent pre-treatment LVEF assessment. Rationale for/against LVEF assessment was rarely documented beyond preparation to receive cardiotoxic chemotherapy. Low CV risk was recorded as rationale for no LVEF assessment in 2 subjects. Among AYAs who underwent pre-treatment LVEF assessment, no significant abnormalities were detected and no changes in subsequent treatment plans were found. During median follow-up of 6.7 (inter-quartile range 5.4-9.5) years, 6/115 (5%) experienced CV events. Only 2 (1.7%) survivors experienced potential anthracycline-related CV events: 1 moderate cardiomyopathy at 9 years, 1 peri-partum cardiomyopathy and atrial fibrillation due to post-radiation SVC occlusion at 15 years post-treatment. Both these AYAs (aged 38 and 31 years at time of CV events) also had other CV risk factors - family history, smoking, obesity, hyperlipidemia. Four (3.5%) survivors' experienced CV events (1 sinus tachyarrhythmia, 1 junctional rhythm, 2 acute/asymptomatic drop in LVEF) unrelated to anthracyclines with clear alternative etiology e.g. sepsis/symptom burden. There was no correlation between having pre-treatment LVEF assessment and occurrence of CV events. 13/115 (11.3%) developed new CV risk factors: 4 hypertension, 6 hyperlipidemia, 3 diabetes.

CONCLUSIONS: Pre-treatment LVEF assessment is inconsistently performed in AYA lymphoma patients and is largely standard of care but does not impact initial treatment or predict late cardiotoxicity. CV events in long-term AYA lymphoma survivors are rare but

evaluation of CV risk factors, early detection and management may be more important than focusing on LVEF assessment.