JACC: CARDIOONCOLOGY VOL. 6, NO. 2, 2024

EDITORIAL COMMENT

Anthracyclines in Older Adults With Hodgkin Lymphoma

Too Much, Too Little? Getting it Just Right*

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Hodgkin lymphoma (HL) is curable in most patients, but 10% to 30% of patients who receive standard therapy will develop relapsed or refractory disease.[1] Although older adults constitute only 20% of incident HL cases, they disproportionately represent more than 60% of HL-related deaths.[2] It remains unclear if these differences are due merely to more aggressive biology of disease in older adults (with an increased incidence of mixed cellularity histology, Epstein-Barr virus-related, and advanced-stage disease)[2] or whether other factors contribute, such as unequal treatment.

Selection of chemotherapy for all patients with HL, regardless of age, includes careful evaluation of functional status, comorbidity, goals, and values. Treatment of fit older adults with HL is given with curative intent. This entails combination chemotherapy, incorporating an anthracycline, a cardiotoxic agent that may result in cardiomyopathy.[3,4] Anthracycline-related cardiac events may occur in up to 65% of patients, with the total cumulative dose being one of the strongest predictors.[5]

Although older adults with cancer who receive chemotherapy are more vulnerable to treatment-related toxicity and associated harm, numerous studies have demonstrated that fit older adults receive the same benefit from standard-of-care treatment as younger patients.[6] Unfortunately, data on tolerability are less clear, as older adults, especially those who are vulnerable or frail, are underrepresented in clinical trials. Comprehensive geriatric assessment (CGA) is the standard of care for older adults with cancer.[7] It offers a more complete understanding of patient fitness, mitigates the risk for over- and undertreatment, and tailors supportive care interventions.

In this issue of *JACC: CardioOncology*, the paper by Upshaw et al[8] offers insights into the realities of treatment for older patients in a real-world setting. First, it is worth noting that in the Eastern Cooperative Oncology Group study (E2496) that established doxorubicin, bleomycin, vinblastine, and dacarbazine as the standard of care for advanced-stage HL, the median age was 33 years.[9] Yet in this study, patients receiving treatment in the community were often 40 years older than those in the seminal clinical trials.[8] Second, in the E2496 clinical trial, 84% of patients >60 years of age received at least 1 dose reduction, and only 73% of patients were able to maintain dose intensity. Five-year overall survival was significantly inferior compared with that of younger patients (58% vs 90%), and the incidence of death without progression was also increased in older patients (22% vs 9%).[10] These were patients fit, healthy, and well resourced enough to enroll in a clinical trial, and they serve as a reminder of the challenge of tolerability and competing risks in older adults with cancer.

The data from the Upshaw et al[8] investigation also highlight other challenges. Cardiovascular

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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Husam Abdel-Qadir, MD, PhD, served as Guest Associate Editor for this paper. Paaladinesh Thavendiranathan, MD, MSc, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.03.003

comorbidities were prevalent, with substantial rates of heart failure (13.1%), coronary artery disease (29%), and atrial fibrillation (13.4%). Patients with pre-existing heart failure were less likely to receive anthracycline treatment (OR: 0.42; 95% CI: 0.29-0.60) and faced a heightened risk for cardiovascular mortality (HR: 3.36; 95% CI: 2.61-4.31). Despite the risks inherent within the subset of patients with heart failure, anthracycline use was associated with reduced lymphoma mortality (HR: 0.44; 95% CI: 0.28-0.71), without an accompanying increase in cardiovascular mortality. The risk for lymphoma-related mortality surpassed that for cardiovascular-related mortality by 3 to 4 times in the initial 5 years post-diagnosis, even among those with pre-existing heart failure. This reminds us of the importance of carefully considering disease-related mortality for patients with HL and comorbid heart failure.

Among patients with heart failure at the time of HL diagnosis, approximately one-half were prescribed beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, which may be due to many different factors. As noted by the investigators, one of the limitations of the retrospective nature of this analysis was the lack of ejection fraction data for the population, which limits the ability to draw conclusions about the reasoning behind prescribing patterns and the clinical decision making of the physicians caring for the patients.

What are the take-home points from this study, and how does it inform oncologic care in the clinic? First, eliminating inequities for older adults with HL by increasing enrollment of older adults, without the exclusion of common comorbidities such as heart failure, in clinical trials is a top priority. It is challenging in the clinic to answer common questions regarding tolerability, the likelihood of adverse events, and prognosis without clinical trial data. Second, decisions regarding treatment are potentially influenced by clinician bias, as demonstrated by the overall low use of anthracyclines for older adults with potentially curable cancer. Third, cardiovascular toxicity remains the leading cause of nononcologic morbidity and mortality among cancer survivors. Although academic centers are at the forefront of cardio-oncology program development, the majority of patients with cancer across the country receive their cancer care and cardiac care in their local communities. Patients are likely to benefit from enhanced care coordination, led by cardiologists' collaboration in the comanagement of patients with cancer before, during, and after treatment for cancer.

When making decisions on how to best care for older adults with cancer, it is crucial to understand that a patient's functional age may differ from their chronological age. Tools such as CGA and related scores, such as the Cancer and Aging Research Group chemotherapy score, are instrumental in customizing care and assessing toxicity risk. Over the past decade, CGA has influenced treatment strategies, guiding adjustments in chemotherapy intensity and the provision of additional support. This comprehensive evaluation assesses various domains such as comorbidity, functional status, cognitive function, psychological well-being, nutrition, medication use, and social support. The benefits for patients include potential life extension, maintenance of quality of life and function, reduced acute care use, and greater satisfaction of care for both patients and caregivers.[11-13]

It is worth noting that an added limitation of Surveillance, Epidemiology, and End Results data are how patient preferences influence treatment decisions. Older adults often have different goals and priorities, and selecting maintenance of function or quality of life may be as or more important than maximizing survival.[14] Therein lies the "Goldilocks principle," as we consider how to interpret care quality in the study by Upshaw et al.[8] As we know from Goldilocks's adventures in the home of the three bears, the porridge was too hot, too cold, or just right. Likewise, older adults with HL with concomitant cardiac disease may be undertreated or overtreated. CGA, cardio-oncology care coordination, and eliciting patient goals and preferences can make things just right.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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JACC: CARDIOONCOLOGY, VOL. 6, NO. 2, 2024
APRIL 2024:214–216

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KEY WORDS geriatric assessment, geriatric oncology, lymphoma, precision oncology