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Cardiovascular Concerns, Cancer Treatment, and Biological and Chronological Aging in Cancer

JACC Family Series

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ABSTRACT

Cardiovascular disease (CVD) and cancer are leading causes of death globally, particularly among the rapidly growing population of older adults (OAs). CVD is a leading cause of mortality among cancer survivors, often accelerated by cancer treatments associated with short- or long-term cardiotoxicity. Moreover, there is a dynamic relationship among CVD, cancer, and aging, characterized by shared risk factors and biological hallmarks, that plays an important role in caring for OAs, optimizing treatment approaches, and developing preventive strategies. Assessment of geriatric domains (eg, functional status, comorbidities, cognition, polypharmacy, nutritional status, social support, psychological well-being) is critical to individualizing treatment of OAs with cancer. The authors discuss considerations in caring for an aging population with cancer, including methods for the assessment of OAs with CVD and/or cardiovascular risk factors planned for cancer therapy. Multidisciplinary care is critical in optimizing patient outcomes and maintaining quality of life in this growing vulnerable population. (J Am Coll Cardiol CardioOnc 2024;6:143-158) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cancer and cardiovascular disease (CVD) are age-related diseases whose increasing prevalence parallels the aging population. The older U.S. population (≥65 years of age) grew 5 times faster than the general population over the past century, with the fastest growth over the past decade, driven by the aging of baby boomers. Older adults (OAs) represent nearly 17% of the U.S. population and have a life expectancy of 76.4 years.[1] CVD incidence and prevalence rise significantly with age, with 80% of CVD-related deaths among individuals ≥65 years of age.[2] OAs are estimated to represent 60% of patients with new cancer diagnoses by 2035, and recent U.S. data predict that 1 in 3 adults aged ≥70 years will develop invasive cancer.[3,4] Moreover, the number of cancer survivors has grown as cancer screening, diagnosis, and treatment improve, with 67% of 18 million American cancer survivors aged ≥65 years in 2022.[5] Understanding the interplay between CVD and cancer, 2 major health concerns affecting OAs and the 2 leading causes of death in the United States, is vital for developing a holistic treatment approach for OAs with cancer that includes early intervention and targeted preventive strategies.[1]

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ABBREVIATIONS AND ACRONYMS

ADL = activities of daily living

AE = adverse event

CTR-CVT = cancer therapy-related cardiovascular toxicity

CV = cardiovascular

CVD = cardiovascular disease

GA = geriatric assessment

HER2 = human epidermal growth factor receptor 2

HF = heart failure

HTN = hypertension

NCCN = National Comprehensive Cancer Network

OA = older adult

QOL = quality of life

AGING, CVD, AND CANCER: SHARED RISKS AND BIOLOGY

CVD risk is closely linked to age-related structural and functional changes in the cardiovascular (CV) system. These changes are compounded by risk factors that are more prevalent with age, such as hypertension (HTN), hyperlipidemia, obesity, and diabetes.[6] Chronic inflammation is a crucial pathophysiological link between CVD and cancer, contributing to the development and progression of atherosclerosis and carcinogenesis.[7] The chronic proinflammatory state seen with aging, often referred to as "inflammaging," is associated with increased morbidity and mortality in OAs and has been implicated in many age-related diseases, including CVD and cancer.[7] It likely derives from accumulated cell damage, microbiome by-products, cellular senescence (terminal cell-cycle arrest), and immune dysregulation.

Several cellular mechanisms lie at the intersection of aging, cancer, and CVD. Hallmarks of aging include cellular senescence, altered intracellular communication, mitochondrial dysfunction, genomic instability, epigenetic changes, telomere attrition, and stem cell exhaustion.[8] These hallmarks overlap with hallmarks of cancer, particularly the accumulation of mutations, cellular damage, decreased immune function, and, most important, cellular senescence.[9] Cellular senescence, an irreversible cell-cycle arrest frequently seen in aging tissues, is provoked when telomeres reach a critically short threshold. Proliferation beyond this limit drives further telomere erosion, ultimately triggering chromosomal instability. Short telomere length has been implicated in inherited syndromes associated with accelerated aging and increased cancer risk, likely as a result of DNA damage, as well as many age-related diseases (eg, CVD, diabetes).[9] For instance, accumulating senescent cells contribute to vascular dysfunction, leading to CV aging and increased risk for CVD.[10] Although short telomere length is associated with increased cancer risk, many cancers upregulate telomerase, an enzyme that counteracts further telomere shortening, thereby evading cell death in the face of critically short telomeres.[9] Mitochondrial dysfunction, another hallmark of aging, has similarly been implicated in the pathogenesis of both CVD and cancer through oxidative stress and accelerated apoptosis or resistance to apoptosis, respectively.[10,11]

HIGHLIGHTS

- Cardiovascular disease (CVD) and cancer, two major diseases affecting the growing number of older adults (OA), have a bidirectional relationship with shared risk factors and biological hallmarks.
- Care of OA with cancer requires a comprehensive geriatric assessment (GA), which evaluates several domains that are relevant to management, outcomes, and quality of life (QOL) of patients.
- CVD and cardiovascular (CV) risk factors increase the risk of cancer therapy-related cardiovascular toxicity (CTR-CVT) in OA with cancer, making the overall care of these vulnerable patients more complex.
- Multidisciplinary care that incorporates the risk of CVD and CTR-CVT in the overall assessment of OA with cancer is critical to minimizing and preventing complications, and maintaining QOL.

Aging has long been considered a driver of cancer, as evidenced by the increasing incidence of cancer with age; however, growing data demonstrate a bidirectional relationship, in which cancer and cancer therapies also drive aging and induce cellular senescence. The recently proposed aging-cancer cycle suggests a dynamic relationship in which aging contributes to a "protumorigenic environment," while cancer and cancer treatments accelerate aging in survivors, as evidenced by increased frailty and comorbidities compared with age-matched cancer-free control subjects.[12] Shenoy et al[13] described this as a "snowball effect," in which baseline age-related risk factors are set in motion by a cancer diagnosis and gain momentum with direct toxicity of cancer treatment, associated lifestyle changes, and polypharmacy, leading to CVD.

Although often viewed as distinct medical conditions, CVD is associated with increased cancer risk, just as cancer and its treatments increase CVD risk.[14] Considering the increased risk for CVD among OAs and the growing number of OAs with cancer, long-term toxicity of cancer treatments, particularly CV effects, must be considered. Cancer survivors, many of whom are older, have an increased risk for CVD compared with the general population, making CVD

the leading cause of noncancer death among these patients, often a consequence of cancer therapies.[15] All-cause mortality is significantly worse among cancer survivors who develop CVD compared to those without CVD (5-year overall survival, 75% vs 87%; 8-year overall survival, 60% vs 81%; $P < 0.10$).[16] These statistics highlight the critical need to address CV risk and cancer therapy-related CV toxicity (CTR-CVT) in this rapidly growing population. Moreover, OAs often face unique challenges when managing CVD and cancer concurrently. Comorbidities, frailty, and polypharmacy complicate treatment decisions and increase associated toxicities (**Central Illustration**). Therefore, comprehensive risk assessment and management strategies that address both conditions and associated risk factors are critical. The intersection of CVD and cancer in OAs challenges conventional approaches to these conditions as separate entities, while also offering potential therapeutic targets, treatment optimization, and early intervention.

KEY CLINICAL CONSIDERATIONS IN THE CARE OF OAs WITH CANCER

The care of OAs with cancer is complex and requires a holistic approach, particularly when considering potential risks and benefits of cancer treatment. Evidence-based and geriatric-specific approaches are necessary for informed decision making and to improve clinical outcomes, including quality of life (QOL). However, optimal management of OAs with cancer is limited by a paucity of prospective data because of the underrepresentation of OAs in clinical trials. A recent systemic review found that patients ≥70 years of age constituted only 24% of U.S. Food and Drug Administration clinical trial participants and <10% of National Cancer Institute study participants.[17] Moreover, OAs enrolled in these trials are carefully selected and are often healthier and more robust than most OAs with cancer. Age-specific efficacy and adverse events (AEs) are also underreported in phase 3 trials, making it difficult to extrapolate whether prospective data are generalizable to OAs.[18] As a result, oncologists often draw from clinical experience and clinical trial data from younger cohorts in developing treatment plans for OAs. Notably, emerging data on barriers to clinical trial accrual of OAs have served as a launching pad for the significant effort by the National Cancer Institute to promote and enhance accrual of OAs through clinical trial design and use of geriatric assessment (GA).[19]

A multidimensional evaluation of OAs with cancer is critical in understanding overall health, appropriateness for treatment, risk for treatment-related toxicities, identifying potentially modifiable geriatric abnormalities, need for treatment adjustments, and predicting morbidity and mortality. This is especially important to OAs, who often value QOL over longevity, particularly if treatment-related toxicities carry a risk for functional impairment, cognitive impairment, or loss of independence.[20] Multiple domains are affected by aging that affect outcomes among OAs with cancer and may be missed on routine oncologic evaluation: functional status, comorbidities, cognition, polypharmacy, nutrition, geriatric syndromes (eg, falls, frailty, osteoporosis, fatigue), social support, and psychological distress[21] (**Table 1**).

FUNCTIONAL STATUS. Functional status, which generally refers to strength, mobility, and ability to live independently, is highly variable between aging individuals and is affected by more than chronological age alone. Assessing physical function is critical for cancer treatment decisions, including whether treatment is appropriate, if dose modifications are necessary, and for predicting treatment tolerance. Although Eastern Cooperative Oncology Group performance status and chronological age are commonly used as surrogates of functional status in determining the most appropriate therapy for an older patient, they seldom reflect a patient's true biological age given subjectivity and interobserver variability of performance status assessment, as well as significant heterogeneity in fitness and comorbidities among patients of similar age.[22] Self-reported measures of functional status can be helpful in assessing fitness and mobility. They consist of activities of daily living (ADL; basic self-care skills such as bathing, dressing, and feeding) and instrumental ADL (complex skills required for independent living such as shopping, medication management, and managing finances). The Short Physical Performance Battery and the timed up and go test, which assess balance, mobility, and strength, are predictive of survival, treatment tolerance, and functional decline.[23] The National Comprehensive Cancer Network (NCCN) recommends using an objective measure of physical function and mobility in addition to self-reported ADL and instrumental ADL when assessing the functional status of OAs with cancer.[24,25]

COMORBIDITIES. Compared with aged-matched control subjects, OAs with cancer are more likely to have multiple comorbidities as they age, including CVD, HTN, diabetes, chronic kidney disease, arthritis, osteoporosis, and cognitive impairment. Comorbidities can represent a competing risk of death for an OA with cancer and are associated with inferior QOL, decreased receipt of anticancer therapy, increased

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CENTRAL ILLUSTRATION **Considerations in Older Adults With Cancer and Cardiovascular Disease Overlapping**

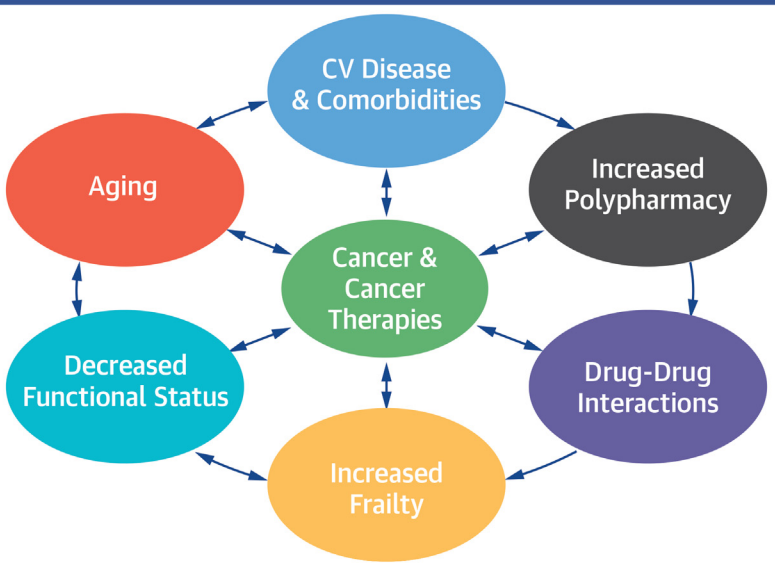
A Factors Impacting Care of Older Adults With Cancer and Comorbid CV Disease

Cardiac-Related Factors	Impact
CV-associated comorbidities (HTN, DM, obesity)	Polypharmacy
CVD	↑ Frailty & falls

Age-Related Factors	Impact
Comorbidities	↑ Frailty & polypharmacy
Altered drug metabolism & impaired organ function	↑ Risk of drug-drug interactions → ↑ frailty & ↓ functional status
Aging	↓ Functional status & cognition
Lack of social support	↓ Access to care
Financial toxicity	↓ Compliance

Cancer-Related Factors	Impact
Teatment-related side effects	Polypharmacy, frailty, & ↓ functional status & cognition
Malnutrition & cachexia	Sarcopenia, frailty, & ↓ mobility & functional status

B Cycle of Frailty in Older Adults With Cancer and CV Disease



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(A) Effects of cardiovascular disease (CVD), cancer, and cancer therapy on geriatric domains. Cancer, cancer therapies, and CVD have overlapping effects on geriatric domains. The intersection of these comorbidities complicates the care of older adults with cancer. Multiple factors affect the care of older adults with CVD, including age-related, cancer-related, and cardiovascular factors. Geriatric assessment can identify changes in these geriatric domains and offer potential interventions to improve patient outcomes. (B) Cycle of frailty in older adults with cancer and CVD. There is dynamic relationship among cancer, cancer therapies, and geriatric domains in older adults with cancer and CVD, represented here as a cycle of frailty. This highlights the nuanced approach necessary in managing this growing patient population. CV = cardiovascular disease; DM = diabetes mellitus; HTN = hypertension.

TABLE 1 Geriatric Domains, Assessment Tools, and Interventions for OAs With Cancer[24]

Domain	Geriatric Assessment Tools	Evaluation	Interventions
Functional status	ADL: Katz index IADL: Lawton-Brody scale Short Physical Performance Battery Timed up and go test	Dependence with ADL and/or IADL Combined score ≤9 Time >13 seconds	• Prehabilitation • Consider cardiac rehabilitation if comorbid cardiovascular disease and/or risk factors • Physical and/or occupation therapy
Comorbidities	Cumulative Illness Rating-Geriatric	Comorbid conditions including hearing and/or visual impairment	• Treat and optimize comorbid conditions in coordination with other providers • Screen for potential confounders (eg, depression, fatigue, nutritional deficiency, endocrine dysfunction, substance use disorder)
Cognition	Mini-Cog	Memory loss, confusion, abnormal screening (Mini-Cog score <4, BOMC test score ≥4)	• Assess decision-making capacity • Further cognitive testing • Close medication reconciliation • Consider neuropsychiatric referral
Polypharmacy	Beers criteria Medication Appropriateness Index	Use of ≥5 prescribed medications	• Close medication reconciliation • Review drug interactions and consider deprescribing at regular intervals • Assess potentially inappropriate medications for OAs (eg, anticholinergic drugs, long-acting benzodiazepines)
Nutrition	MNA	>3-kg unintentional weight loss in 3 mo, BMI ≤21 or ≥30 kg/m^2	• Referral to registered dietician • Diet and supplement recommendations to prevent nutritional deficiencies, maintain a healthy weight, and optimize caloric intake • Consider referrals to speech pathology and/or occupational therapy if difficulty with swallowing, eating
Geriatric syndromes	Balducci frailty criteria Bone health screening Fall risk assessment	Repeated falls (>3 in 6 mo), severe urinary/fecal incontinence affecting ADL, osteoporosis	• Optimize bone health • Function status assessment • Physical and/or occupation therapy • Home safety evaluation
Social support	Assess primary caregiver(s), living conditions, financial concerns, transportation needs	Lack of social support, living alone, financial toxicity	• Review and complete advanced directive • Identify health care proxy and caregiver(s) • Referral to social work and home health services • Home safety evaluation • Screen for elder abuse • Consider counseling
Psychological distress	NCCN Distress Thermometer Geriatric Depression Scale	Depression, anxiety, adjustment disorder	• More in-depth evaluation if positive screening results • Referral to psychosocial services • Consider chaplain referral per patient beliefs
Geriatric Assessment Tools			
	Objective	Clinical Factors	Scores and Recommended Intervention
G8 geriatric screening tool	Determines which patients would benefit from a full geriatric assessment	Decreased food intake, recent weight loss, mobility, neuropsychological problems (eg, depression, dementia), BMI, polypharmacy (>3 medications/d), perceived health status	Comprehensive geriatric assessment recommended for patients with scores ≤14, which indicates vulnerability
CARG toxicity prediction tool	Graded risk of severe treatment-related adverse effects	Age, gastrointestinal or genitourinary cancer, single or multiagent chemotherapy, dose attenuation, renal function, hearing impairment, falls, assistance with medication management, mobility, impact of health on social activity	Score 0-5: 30% risk (low) Score 6-9: 52% risk (intermediate)[a] Score 10-23: 83% risk (high)[b]
Chemotherapy Risk Assessment Scale for High-Age patients (CRASH)	Graded risk of hematologic and nonhematologic treatment-related adverse effects	Hematologic: diastolic blood pressure, IADL, lactate dehydrogenase, chemotherapy toxicity score	Hematologic score: 0 or 1: low risk; 2 or 3: low to intermediate risk[a]; 4 or 5: intermediate-high risk[b]; ≥6: high risk[b]
		Nonhematologic: ECOG performance status, Mini-Mental State Examination, MNA, chemotherapy toxicity score	Nonhematologic score: 0-2: low risk; 3 or 4: low to intermediate risk[a]; 5 or 6: intermediate to high risk[b]; ≥8: high risk[b]
			Combined score: 0-3: low risk; 4-6: low to intermediate risk[a]; 7-9: intermediate to high risk[b]; ≥10: high risk[b]

[a]Consider dose modification and/or closer toxicity monitoring. [b]Consider dose modification with closer toxicity monitoring or best supportive care.

ADL = activities of daily living; BMI = body mass index; BOMC = Blessed Orientation-Memory-Concentration; CARG = Cancer and Aging Research Group Chemotherapy; ECOG = Eastern Cooperative Oncology Group; IADL = instrumental activities of daily living; MNA = Mini Nutritional Assessment; NCCN = National Comprehensive Cancer Network; OA = older adult.

treatment-related toxicity, treatment delays or modifications, and higher all-cause mortality.[26-28] Assessing the number and severity of comorbidities in OAs with cancer as well as their impact on functional status is essential in formulating and tailoring a cancer treatment approach. There are several comorbidity indexes that predict treatment tolerance, risk for treatment discontinuation, and survival, though most were validated for patients without cancer, and results vary according to disease type. A recent study showed that the Cumulative Illness Rating Scale-Geriatric, a weighted index of comorbidities by organ system, was most prognostic for 1-year mortality among OAs with metastatic cancers.[29] The Cumulative Illness Rating Scale-Geriatric, which can also predict treatment tolerance, is one of the most sensitive and commonly used measures of comorbidities in OAs with cancer.[27]

COGNITION. Cognitive impairment in OAs with cancer is a risk factor for functional dependence, depression, medication nonadherence, and death.[30] Dementia, defined by progressive cognitive impairment involving 1 or more cognitive domains, is more prevalent in OAs and is a common comorbidity in OAs with cancer. The NCCN recommends screening for cognitive impairment in OAs with cancer using the Mini-Cog test, which consists of a clock drawing test and a 3-word recall, and/or the 6-item Blessed Orientation-Memory-Concentration test, which evaluates orientation, concentration, and memory.[24,25] Further evaluation is recommended if new cognitive impairment is identified, including screening for potential confounders such as depression, fatigue, nutritional deficiency, endocrine dysfunction, substance use disorder, and polypharmacy. Importantly, cancer treatments such as chemotherapy and brain radiation can contribute to or precipitate cognitive decline. Periodic cognition assessment to screen for new or worsening cognitive impairment is recommended for OAs with cancer who have previously received cancer treatment or are on active treatment. Ensuring appropriate social support at home and addressing advanced care planning (eg, advanced directives, designating a health care proxy) are also recommended for OAs with identified cognitive impairment. Targeted interventions such as cognitive rehabilitation have not been studied in OAs with cancer, particularly among those with baseline cognitive impairment.

POLYPHARMACY. Polypharmacy, or the use of ≥5 medications, is common in OAs and is closely linked to comorbidities. It can result from the addition of medications to control cancer treatment-related symptoms such as nausea, vomiting, diarrhea, constipation, or HTN. Although it may be clinically appropriate and/or necessary, polypharmacy is associated with increased drug interactions, treatment-related AEs, frailty, and medication nonadherence.[31] This risk also stems from altered drug metabolism in OAs due to age-related physiological changes and impaired organ function. A comprehensive review of patient medications, including assessing potentially inappropriate medications for OAs (eg, anticholinergic drugs, long-acting benzodiazepines), should be performed periodically, and deprescribing medications should be considered.[32] Two of the most commonly used tools for polypharmacy assessment are the Beers criteria and the Medication Appropriateness Index, though a validated method to better define polypharmacy and appropriate interventions in this patient population is needed.[33]

NUTRITIONAL STATUS. Poor nutritional status and weight loss are significant risk factors for treatment-related toxicity as well as increased cancer-specific and overall mortality in OAs.[34] Cancer is often responsible for malnutrition through catabolism and metabolic dysregulation, leading to anorexia and cachexia. Decreased nutritional intake in this setting often compounds underlying age-related sarcopenia (loss of muscle mass) and often translates to increased frailty.[35] The Mini Nutritional Assessment is a validated screening tool that identifies malnutrition or risk for malnutrition by assessing changes in food intake, recent weight loss, mobility, psychological distress, dementia, and body mass index. Appetite stimulants and anticachexia drugs are not routinely used in clinical practice because of limited efficacy as well as possible toxicities (eg, thromboembolism with megestrol; altered mental status, muscle wasting, and adrenal insufficiency with prolonged steroid use).[36] There are emerging data on the use of medical marijuana as an appetite stimulant, as well as an antiemetic and analgesic agent; however, further research is needed, particularly in OAs whose other geriatric syndromes make this approach risky.[37] Collaboration with a registered dietician and a patient's social support system or caregiver are important tools to prevent nutritional deficiencies, maintain a healthy weight, and optimize caloric intake.

GERIATRIC SYNDROMES. Geriatric syndromes are multifactorial clinical conditions that are more prevalent with increasing age. They include frailty, fatigue, osteoporosis, incontinence, delirium, and falls. Frailty, a syndrome defined by decreased physiological reserve, is associated with falls,

decreased mobility, dependence with ADL, and increased comorbidities. Unlike many other assessment tools that have been developed to evaluate frailty, the Balducci frailty criteria, which are based on a comprehensive GA, are specific to OAs with cancer.[38] This model defines predictors of frailty as age ≥85 years, dependence for ≥1 ADL, ≥3 comorbidities, and ≥1 geriatric syndrome. Cancer-related fatigue is common among patients with cancer, exacerbated by treatment and refractory to rest and sleep.[39] As a result of fatigue, OAs with pre-existing vulnerabilities may experience further declines in geriatric domains, particularly functional status and independence. Osteoporosis is another major issue for OAs with cancer, particularly with a concurrent risk for falls and with cancer treatments that promote loss of bone density and muscle mass (eg, hormonal therapies, steroids). Optimizing bone health through appropriate screening, vitamin D supplementation, and bone-modifying agents as indicated is essential in the care of OAs with cancer and cancer survivors. This is particularly important considering that falls are another major health concern for OAs and are more common in OAs with cancer than cancer-free OAs. Fall risk can increase because of cancer, treatment-related fatigue, sarcopenia, peripheral neuropathy caused by therapy, and weakness.[31] The timed up and go test or measuring gait speed are simple tools to assess balance and fall risk.[40] Minimizing risk of falls by promoting exercise, optimizing home safety, minimizing polypharmacy, and discontinuing sedating or psychotropic medications, is a critical aspect of comprehensive geriatric care.

SOCIAL SUPPORT. Reliable social support is also fundamental to optimizing treatment outcomes in OAs with cancer. Reviewing a patient's living conditions, financial status, transportation options, and potential caregivers will help identify and preempt potential barriers to effective care. Advanced care planning, referrals to social work, and obtaining home health assistance are critical in facilitating treatment plans and optimizing patient outcomes. The NCCN OA Oncology Panel also recommends a social work referral to evaluate these aspects of social support, as well as to assess home safety and screen for elder abuse.[24]

PSYCHOLOGICAL DISTRESS. Psychological distress, including depression, anxiety, and adjustment disorder, is reported in approximately 40% OAs with cancer.[41] A prospective study of OAs with recently diagnosed cancer showed that depression was independently associated with impaired functional status, cognitive impairment, comorbidities, polypharmacy, and inadequate social support.[42] In turn, psychological distress is associated with decreased QOL, increased symptom burden, increased risk for hospitalization, and inferior survival.[31] The Geriatric Depression Scale is a tool to screen for depression in OA without severe cognitive impairment, and truncated versions have been validated for screening. The NCCN Distress Thermometer screens for physical, functional, emotional, social, and spiritual concerns and should be paired with a more in depth evaluation for OA who have positive screening results, as well as referral to psychosocial services.[43]

In summary, the care of OAs with cancer is complex and nuanced, as these geriatric domains are intertwined: a change in one often has a ripple effect on other aspects of geriatric health (**Central Illustration**). Cancer and cancer treatments can affect all of these domains, leading to increased frailty, poor treatment tolerance, and inferior outcomes. For example, neuropathy or cognitive impairment from cancer treatment can lead to increased risk for falls in an already vulnerable OA, which cascades to potential fractures, decreased mobility and functional status, loss of independence, and inability to receive further treatment because of worsening frailty. Similarly, treatment that can cause CV toxicity (eg, heart failure [HF], HTN, thromboembolism, arrhythmias, hypotension) can complicate treatment approaches and outcomes in OAs with cancer who have or are at high risk for comorbid CVD. These complications may lead to increased frailty, hospitalization, increased polypharmacy, and often cancer treatment discontinuation or delay. Alternatively, concerns for specific treatment-related toxicity or limited functional reserve in OAs with cancer and multiple comorbidities complicate treatment decisions and often necessitate treatment modification. For example, comorbid diabetes-related peripheral neuropathy may preclude some OAs from chemotherapies that can worsen neuropathy (eg, oxaliplatin for gastrointestinal malignancies and taxanes for breast cancer) despite their proven efficacy in those diseases.

PERSONALIZING CARE OF OAs USING GA

Given the relationship between these geriatric domains to cancer care and oncologic treatment decisions, considering vulnerabilities revealed through comprehensive GA often influences treatment recommendations and goals of care. Weighing the risks and benefits of cancer treatments in this patient population is challenging, as treatment-related complications can be more severe because of age- and disease-related physiological changes, leading to

worsening comorbidities, functional status, QOL, and survival. GA can further inform shared decision making by assessing appropriateness for treatment, predicting treatment-related toxicities, and identifying modifiable geriatric factors that improve treatment outcomes (**Table 1**).

Several studies have demonstrated that GA-based interventions and cancer care decrease functional decline, hospitalizations, and mortality.[44-46] However, time and personnel constraints remain barriers to the widespread adoption of GA-guided cancer care.[47] GA screening tools and chemotherapy toxicity prediction calculators offer faster, simplified evaluations of OAs with cancer. The G8 geriatric screening tool identifies OAs with cancer who would benefit from a comprehensive GA, which remains the gold standard for a complete evaluation of this patient population (**Table 1**).[48] The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) and Cancer and Aging Research Group Chemotherapy (CARG) toxicity tool are validated to predict the risk for treatment-related toxicity in OAs with cancer.[22,49]

GA influences treatment decisions for OAs with cancer, including changing, intensifying, reducing, or delaying therapy in up to 82% of patients, leading to fewer serious AEs.[50] Chemotherapy deintensification is most common, representing a median 73% of treatment changes in a recent systemic review.[46] GA-driven interventions are associated with a high rate of planned chemotherapy completion, fewer treatment modifications, and decreased toxicity.[51] The GAIN (Geriatric Assessment-Driven Intervention) and GAP70+ (A Geriatric Assessment Intervention for Patients Aged 70 and Over Receiving Chemotherapy or Similar Agents for Advanced Cancer: Reducing Toxicity in Older Adults) trials validated the benefit of GA-guided oncologic care, demonstrating improved treatment tolerance with a 10% to 20% decrease in severe AEs.[52,53] GA-guided care is recommended by the NCCN and the American Society of Clinical Oncology in managing OAs with cancer as it identifies geriatric vulnerabilities, provides prognostic information, and is critical in individualizing and optimizing treatment.[24,54]

However, the Chemotherapy Risk Assessment Scale for High-Age Patients and Cancer and Aging Research Group Chemotherapy tools predict chemotherapy tolerance but do not account for specific disease and treatment variables as they were validated in a heterogenous population of OAs with cancer. The treatment landscape in oncology has dramatically changed with novel therapies since these tools were developed and validated, limiting their broad applicability and highlighting the need for more disease- and treatment-specific tools to maximize the predictive value of GA. The Cancer and Aging Research Group Chemotherapy Breast Cancer score, the only validated disease-specific GA tool thus far, predicts the risk for chemotherapy-related AEs in OAs with early-stage breast cancer.[55] Similarly, geriatric tools and biomarkers to predict CTR-CVT are not available at this time. Ezaz et al[56] developed a proof-of-concept 7-factor risk score on the basis of Surveillance, Epidemiology, and End Results-Medicare claims data to determine the 3-year risk for cardiomyopathy and HF after adjuvant trastuzumab (an anti-human epidermal growth factor receptor 2 [HER2] monoclonal antibody), which requires further validation.

GA also leads to nononcologic interventions aimed at addressing vulnerabilities, including polypharmacy, nutritional support, optimizing comorbidities, and social interventions. A systemic review of 61 geriatric oncology studies revealed that having a prespecified intervention protocol led to nononcologic interventions in more than 70% of patients, compared with 26% in studies that did not.[46] Addressing identified vulnerabilities in cognitive impairment, polypharmacy, mobility, and social support were at least 5 times less likely without a prespecified intervention. GA is also associated with increased advanced care planning and goals of care discussions, as well as improved QOL and physical functioning.[46,57] Additionally, GA and GA-guided recommendations improved both patient and caregiver satisfaction and increased discussion of age-related concerns in vulnerable OAs with cancer in the prospective COACH (Improving Communication in Older Cancer Patients and Their Caregivers) study.[58] These data highlight the importance of using GA and GA screening tools in conjunction with prespecified interventions to optimize treatment approaches, provide holistic care, and improve patient outcomes in OAs with cancer.

RECOMMENDATIONS FOR MANAGING OAs WITH COMORBID CV RISK

Frailty and CVD are closely related, as the prevalence of both increases with age.[59] As such, managing the interaction among CVD, geriatric syndromes, and potentially cardiotoxic cancer therapies necessitates clearer geriatric cardiology and oncology approaches to minimize CV risk in this vulnerable, heterogeneous patient population. Involving a geriatrician in the management of these patients can offer additional support in managing the complex care of OAs with cancer. Improving screening, prevention, and management of CVD in OAs with cancer should aim to

minimize CV complications that can worsen frailty and other geriatric domains, decrease cancer treatment tolerance, and increase mortality.

Although CV toxicities can arise across many different oncologic drug classes and affect patients across the age spectrum, there are some key considerations when planning such therapies for OAs (**Table 2**). Cardiotoxicity prevention strategies in OAs with cancer require CVD risk assessment, careful consideration of cumulative CTR-CVT risk, a plan for CTR-CVT monitoring, and patient education. Ideally, this should be done collaboratively between the oncologist and cardiologist, who develop a plan on the basis of cancer treatment options (ie, cardiotoxicity risk), underlying CVD, CV risk factors, and a baseline CV assessment. Risk factors for CTR-CVT are variable and often associated with increased cumulative dose (eg, anthracyclines), concurrent potentially cardiotoxic systemic therapies, combination of systemic and radiation therapy, radiation therapy field, age of exposure, baseline CVD or CV risk factors (eg, reduced ejection fraction with anti-HER2 monoclonal antibodies or HTN with tyrosine kinase or vascular endothelial growth factor inhibitors). We recognize the need for greater data in OAs, specifically with respect to CV screening, assessment, prevention, and survivorship. In the following discussion, we describe the current state of knowledge as it pertains to the general population in cardio-oncology and how it might apply to OAs.

CV SCREENING, ASSESSMENT, AND PREVENTION. Screening and assessment of CV risk should focus on coronary artery disease, HTN, and HF, as these are the most common long-term sequelae of cardiotoxic cancer therapies. Furthermore, comorbid cardiac conditions and modifiable risk factors, including HTN, hyperlipidemia, diabetes, obesity, and smoking, should be treated and optimized per respective guidelines in OAs at risk for CTR-CVT.[60] Measuring serum cardiac biomarkers (ie, troponin and natriuretic peptide) before treatment can help identify patients at higher risk for CTR-CVT and the development or progression of CVD, as well as those who might benefit from primary cardiotoxicity prevention or closer monitoring on treatment.[61] Several alternative biomarkers have been proposed, though none have been validated in larger patient populations or in OAs. Serum biomarkers should be paired and interpreted with cardiac imaging, primarily echocardiography to assess left ventricular ejection fraction.[62] Baseline electrocardiography and a lipid panel are also recommended in patients with CVD, those with CV risk factors, and/or those being considered for potentially cardiotoxic therapy (**Figure 1**).

We support the use of the Heart Failure Association–International Cardio-Oncology Society pretreatment CV risk assessment tool, which incorporates age, comorbidities, lifestyle risk factors (eg, smoking, alcohol use, obesity), prior cardiotoxic cancer treatment, cardiac biomarkers, lipid panel, electrocardiography, and echocardiography.[63] High-risk or very high-risk patients require cardiology referral and a multidisciplinary discussion of the risk/benefit ratios of potentially cardiotoxic cancer treatments. Moderate risk should prompt closer oncology follow-up, while routine follow-up is appropriate for patients at low risk. Similarly, the European Society for Medical Oncology cardio-oncology guidelines recommend consideration of alternative noncardiotoxic cancer treatments for patients with left ventricular ejection fractions ≤40% to 50%, as well as for those with left ventricular ejection fractions <40% in addition to cardioprotective therapy.[60] Periodic assessment of left ventricular ejection fraction and cardiac biomarkers is recommended, though the duration and frequency of monitoring depend on specific cancer treatment and baseline CV risk.

Primary prevention consists of optimizing baseline CVD or CV risk factors and potentially cardioprotective medications. It should be considered in OAs who are receiving therapies with high cardiotoxic potential or those with pre-existing CVD, as they are at greater risk for CTR-CVT. Primary prevention with cardiac medications (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins) have not consistently shown prevention of CTR-CVT and are not routinely recommended in the absence of other indications.[60] Similarly, primary and secondary prevention of anthracycline-induced cardiomyopathy using angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has yielded mixed results.[64] Lisinopril or carvedilol use during treatment with trastuzumab (anti-HER2 therapy) and anthracycline as primary prevention was effective in minimizing treatment interruptions in trastuzumab therapy; however, there was no difference in CTR-CVT.[65] The prospective SAFE-HEaRT (Cardiac Safety Study in Patients With HER2+ Breast Cancer) trial offers a potential preventive surveillance approach in patients with borderline asymptomatic left ventricular ejection fraction to receive HER2-directed therapies who may have otherwise been precluded from these drugs.[66] Medication-based prevention in patients undergoing pretreatment evaluation for potentially cardiotoxic therapies should be evaluated in a multidisciplinary setting with oncology and cardiology.[63]

TABLE 2 Cancer Treatments and Associated CV Concerns for OAs

Treatment	General Indication(s)	Associated CV Toxicity	Risk in OAs	Recommendations for Modifications and Monitoring	Specific Recommendations for OAs
Anthracyclines					
Doxorubicin, daunorubicin, idarubicin	Multiple cancers: acute lymphoblastic leukemia, bladder, breast, lymphomas	Acute CM (<5%) Arrhythmias, pericarditis, myocarditis, and/or acute HF Chronic CM (≤5%) Dose dependent Dilated CM, HF, arrhythmias	Risk for HF increases with time and age (~5%)[75]	Two-dimensional echocardiography within 1 y of completing anthracycline therapy (high cumulative dose or a low cumulative dose + ≥1 risk factor for HF)[69]	Pegylated liposomal doxorubicin has a safer cardiac toxicity profile and does not affect cancer treatment efficacy[76,77]
Fluoropyrimidines					
5-FU Capecitabine (oral prodrug of 5-FU)	GI malignancies, advanced head and neck cancers GI and metastatic breast cancers; radiosensitizer with radiation therapy	Coronary vasospasm, chest pain, palpitations (<5%) MI and cardiac arrest rare (<2%)[78]	Cardiotoxicity is rare and does not increase based on age alone[79,80]	Screen for CVD and CV risk factors	GA-based dose modification and interventions to assist with patient selection and increase number of patients completing planned treatment without worsening toxcitiy[81,82]
Anti-HER2 therapies					
Trastuzumab	HER2-positive breast, colorectal, GEJ, gastric cancers	Decreased LVEF (2%-5%), severe cardiotoxicity (≤1%)[83]	Risk for cardiotoxicity is similar in OAs and is proportional to treatment duration	Consider primary prevention with lisinopril or carvedilol during treatment with trastuzumab + anthracycline[65] Has been shown to decreased treatment interruptions with trastuzumab alone but not affect cardiotoxicity rates Baseline echocardiography and monitoring every 12 wk during treatment, followed by echocardiography every 3 mo for at least 2 y after completing HER2 therapy[70]	Use GA to determine fitness for therapy Optimize borderline LVEF and careful consideration of CV risk factors Use with caution in OAs who have previously received anthracyclines
Pertuzumab	HER2-positive breast in combination with trastuzumab	No increased toxicity compared with trastuzumab alone[84]	No increased cardiotoxicity compared with trastuzumab alone	Screen for CVD and CV risk factors	Use with caution given increased risk for diarrhea and fatigue in OAs[85]
Trastuzumab emtansine	HER2-positive metastatic breast cancer	Decreased LVEF (≤2%)[86]	No increased cardiotoxicity on the basis of age	Screen for CVD and CV risk factors	Use with caution given increased risk for nausea, diarrhea, skin changes, and fatigue in OAs[86]
Trastuzumab deruxtecan	HER2-positive breast, GEJ, gastric cancers	Decreased LVEF (2%-5%), severe LV dysfunction (0.5%)[87,88]	Age-specific cardiotoxicity data unavailable	Use with caution if underlying lung disease	NA
Targeted therapies					
VEGF inhibitors (bevacizumab, ramucirumab)	Multiple cancers: cervical, colorectal, glioblastoma, hepatocellular, non-small cell lung, ovarian, renal cell	HTN most common; arterial/venous thromboembolism and CM rare[89]	No increased cardiotoxicity on the basis of age[90,91]	Close blood pressure monitoring and management during therapy	Close blood pressure monitoring and management before and during therapy
Tyrosine kinase inhibitors	Multiple cancers: chronic lymphocytic leukemia, chronic myeloid leukemia, hepatocellular, prostate, renal cell	HTN, arrhythmias, arterial/venous thromboembolism, bleeding (rates variable on the basis of drug, dose, and disease)	No increased cardiotoxicity based on age (age-specific data are limited)	Blood pressure monitoring, periodic electrocardiogram based on drug toxicity profile	Close blood pressure monitoring and management before and during therapy

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SURVIVORSHIP RECOMMENDATIONS. Cancer survivors should be regularly assessed and screened for emerging CVD (eg, blood pressure monitoring, diabetes screening, atherosclerotic CVD risk score). The European Society of Cardiology recommends that high-risk or very high-risk patients (on the basis of pretreatment CV risk assessment) undergo CV assessment every 3 months for the first year after treatment and then annually; low- and moderate-risk patients should undergo annual assessment post-treatment.[63] Survivors at high risk for developing CVD on the basis of treatment or disease should also

TABLE 2 Continued

Treatment	General Indication(s)	Associated CV Toxicity	Risk in OAs	Recommendations for Modifications and Monitoring	Specific Recommendations for OAs
Endocrine therapies					
Androgen deprivation therapy: abiraterone, darolutamide, apalutamide, enzalutamide	Prostate cancer	HTN, rarely atrial fibrillation, CAD, acute coronary syndrome[92-94]	No increased cardiotoxicity on the basis of age (age-specific data are limited)	Screen for CVD and CV risk factors; blood pressure monitoring	Consider alternatives to abiraterone, that require concomitant steroid use[92,93] Close monitoring for osteoporosis
Aromatase inhibitors (eg, anastrozole)	Hormone receptor–positive breast cancer	HF, venous thromboembolism, MI rare (<2%)[95]	No increased cardiotoxicity on the basis of age	Screen for CVD and CV risk factors	Close monitoring for osteoporosis
Other therapies					
Immune checkpoint inhibitors	Multiple cancers: colorectal, hepatocellular, melanoma, non-small cell lung, renal cell	Myocarditis, arrhythmias; rarely CM, HF, pericardial disease	No increased cardiotoxicity on the basis of age (age-specific data are limited)	Consider other IO-related toxicities if CV IO toxicity suspected	Use high-dose steroids with caution when treating IO-related toxicity
Chimeric antigen receptor T-cell therapy	Lymphoma, multiple myeloma	Reduced LVEF, arrhythmias, cardiogenic shock, cardiac arrest	Limited data in OAs with mixed results on risk for cardiotoxicity in OAs compared with younger patients	Cardiac evaluation and optimization in all patients	Cardiac evaluation and optimization and GA-guided care
RT	Multiple cancers	CAD, pericardial disease, aortic regurgitation, aortic stenosis, nonischemic CM	Risk for cardiotoxicity increases with time from RT and increasing age[96]	Modification and toxicity management depend on dose and radiation field; consider intensity-modulated RT to limit toxicity to surrounding tissue or stereotactic body radiation therapy in the palliative setting for shorter, more convenient treatment if medically appropriate	Avoid adjuvant RT for OAs with breast cancer ≥70 years of age[97]

5-FU = fluorouracil; CAD = coronary artery disease; HF = heart failure; CM = cardiomyopathy; CV = cardiovascular; CVD = cardiovascular disease; GA = geriatric assessment; GEJ = gastroesophageal junction; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2; HF = heart failure; HTN = hypertension; IO = immunotherapy; LV = left ventricular; LVEF = left ventricular ejection fraction; NA = not applicable; OA = older adults; RT = radiation therapy; VEGF = vascular endothelial growth factor.

be referred to cardiology for comanagement and HF screening.[67] Aspirin use for secondary prevention and potentially primary prevention may be considered per recommendations from the U.S. Preventive Services Task Force.[68]

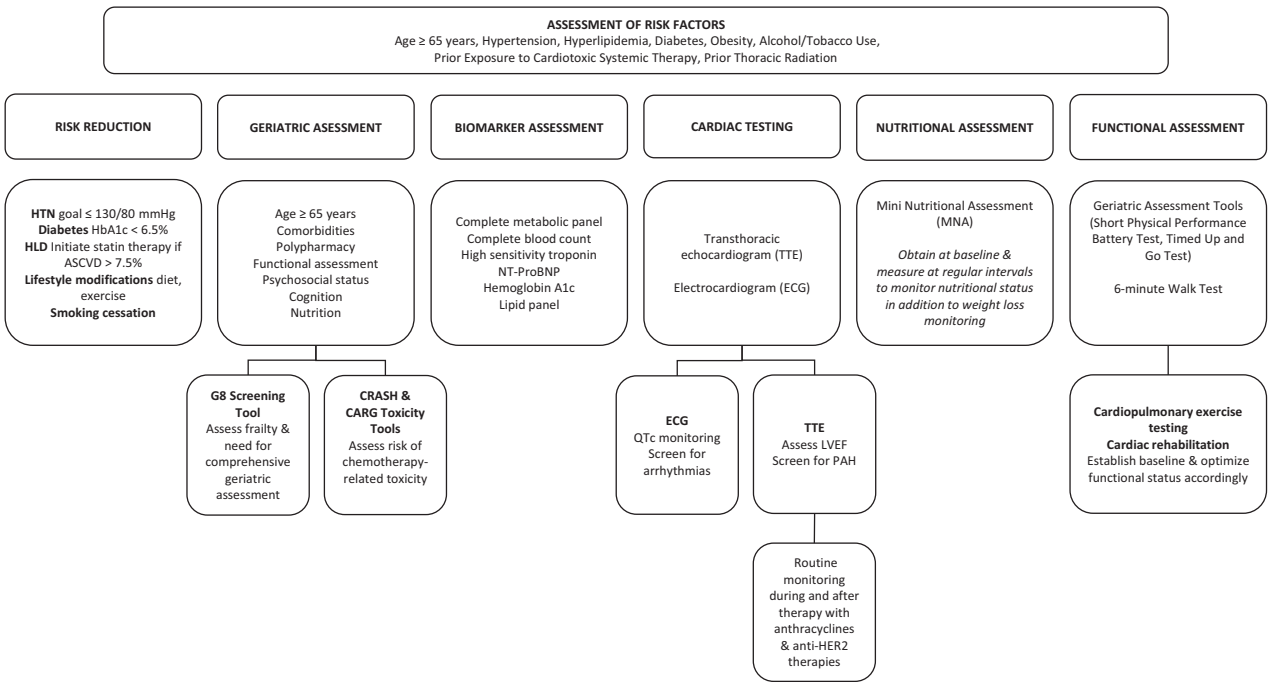
The NCCN survivorship guidelines recommend considering echocardiography within 1 year of completing anthracycline-based therapy or in patients who have ≥1 risk factor for HF.[69] Baseline echocardiography and monitoring every 12 weeks during treatment are recommended with most HER2 therapies, followed by echocardiography every 3 months for at least 2 years after completing HER2 therapy[70] (**Table 2**). Imaging in patients who receive other potentially cardiotoxic therapies should be based on individual risk.

THE INTERSECTION OF GERIATRIC CARDIOLOGY AND GERIATRIC ONCOLOGY

Comorbidities, polypharmacy, and age-related functional and cognitive impairment compound the complexity of pretreatment CV risk assessment in OAs with cancer. As such, GA in this patient population is critical in addition to the CV risk assessment outlined earlier. Most GA screening tools overlap with geriatric cardiology screening tools and are recommended in this patient population, including ADL and instrumental ADL assessment, the Short Physical Performance Battery, the timed up and go test, the Cumulative Illness Rating Scale-Geriatric, the Mini-Cog, the Mini Nutritional Assessment, and the Geriatric Depression Scale.[71]

Assessing polypharmacy, which is associated with frailty, is particularly important in OAs with comorbid cancer and CVD or CV risk factors. Guideline-directed medical therapy for CVD includes several medications, which in addition to those added as supportive care for cancer treatment may increase the risk for adverse drug reactions and interactions. Adverse drug reactions are common causes of emergency department visits or hospitalizations in OAs in the United States, with 42% of emergency department visits resulting in hospitalization because of CV drugs

FIGURE 1 Assessment and Management of Older Adults With Cancer



This algorithm summarizes the authors' recommendations for assessing and managing the care of older adults with cardiovascular disease or risk factors prior to or following cancer treatment. This approach helps identify patients at risk for treatment-related cardiotoxicity and those who may need optimization of cardiovascular factors to prevent other treatment-related adverse effects. ASCVD = atherosclerotic cardiovascular disease risk score; CAD = coronary artery disease; CARG = Cancer and Aging Research Group Chemotherapy; CRASH = Chemotherapy Risk Assessment Scale for High-Age Patients; HbA1c = glycated hemoglobin; HER2 = human epidermal growth factor receptor 2; HLD = hyperlipidemia; HTN = hypertension; LVEF = left ventricular ejection fraction; NT-ProBNP = N-terminal pro-brain type natriuretic peptide; PAH = pulmonary arterial hypertension; QTc = corrected QT interval.

(eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretic agents, antiarrhythmic medications) and 51% related to cancer therapies.[72] Risk for hospitalization for adverse drug reactions increases with age and with polypharmacy (≥5 medications). Polypharmacy is also very common among patients with HF, especially OAs. More than 55% of patients ≥75 years of age with HF were taking ≥10 medications, approximately 20% of whom had comorbid geriatric conditions and about 15% of whom had cancer.[73] Even more OAs (84%) were taking at least 5 medications, which increased to 95% after admission for HF.[73] Notably, most medications were for non-CV indications. Another study failed to demonstrate improved frailty scores with decreasing antihypertensive medications in OAs ≥80 years of age, suggesting that focusing on noncardiac medications may be more beneficial in this population when optimizing polypharmacy.[74] Although there are no clear guidelines for the a priori adjustment of cardiac medications, patients may require drug modifications during cancer treatment to optimize blood pressure, bleeding risk, and/or volume status. The risk for medication-induced hypoglycemia, which can lead to falls, syncope, and hospitalization (emergency department visits or hospitalization related to insulin, 13.9%; oral hypoglycemic agents, 10.7%), is also an important consideration in OAs with cancer, who may have oscillating glycemic control needs in the setting of poor appetite and altered metabolism due to malignancy.[72] Close medication reconciliation, review of drug interactions, and considering deprescribing at regular intervals is critical in preventing functional decline, AEs, and worsening frailty in this vulnerable population.

Functional status, mobility, and strength are also important in assessing OAs with cancer and CVD. Falls are higher in adults with CVD, a risk compounded by aging-related physiological changes (eg, sensory impairment, cognitive impairment, reduced autonomic reflexes, impaired volume homeostasis) and polypharmacy.[71] Assessing functional status and

screening for falls can be important, and simple tools in preventing progressive frailty and AEs during cancer treatment. Additionally, some evidence in OAs without cancer suggests that cardiac rehabilitation may prevent or reverse frailty, as well as improve functional status as measured by the timed up and go test and the Short Physical Performance Battery.[59]

Interval assessment of these domains during and after cancer treatment, particularly functional status and polypharmacy, in addition to serial biomarker and imaging, may offer valuable information before CTR-CVT or treatment-related decline in geriatric domains become clinically apparent or significant.

CONCLUSIONS

Caring for OAs with cancer requires carefully balancing the risks and benefits of cancer therapy, comorbidities, associated toxicities, and other geriatric factors. As the number of OAs with cancer undergoing therapy and older survivors continues to rise, we expect to see a parallel increase in CVD incidence related to cancer treatments and underlying aging processes. The use of GA combined with thorough evaluation and optimization of CV risk factors before and after the completion of cancer treatment is critical in tailoring therapy. This personalized approach in a heterogenous population can limit treatment-related toxicity while improving the likelihood of treatment completion. Moreover, GA and GA-guided interventions improve nononcologic outcomes, including advanced care planning, communication, age-related issues, patient satisfaction, and QOL. Further research to identify risk factors and novel management approaches of CVD in patients with cancer and survivors is warranted, with a particular focus on OAs, who account for most patients facing this significant challenge.

Another essential aspect of care of this population is shared decision making involving oncology, cardiology, and potentially geriatrics to discuss treatment choices that maintain good QOL, functional status, and independence. This is particularly important when considering competing risks of death and treatment trade-offs (eg, cancer treatment can potentially prolong life at the expense of worsening CVD). Revisiting questions regarding "what matters" is equally important as interval GA, considering patient goals and priorities may change over time. This holistic, patient-centered multidisciplinary care addresses the complexity of managing these patients as we await prospective data to further hone our treatment approach.

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