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A Change of Heart

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With advances in diagnostic techniques and improvements in curative and palliative treatment, the number of people living with and through cancer is increasing. Experts estimate that more than 15.5 million people with a history of cancer are living in the United States as of January 1, 2016.[1] This number includes both individuals living with active disease and an increasing number of survivors who are disease-free. Of this population, 67% were diagnosed more than 5 years ago, and nearly one-half (47%) are aged 70 years or older. As this population grows, an emphasis on improving the overall well-being of cancer survivors through management of late and long-term treatment effects, promotion of healthy lifestyle behaviors, and coordinated care between providers has been endorsed by the Institute of Medicine.[2] Thus, providers must consider the short- and long-term outcome of patients when addressing the cancer diagnosis.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Survivorship were developed to help navigate the transition from patient with cancer to survivor without cancer, providing guidance for health care providers on approaching many of the issues a survivor may face. For some of the guideline's algorithms, incorporating the outlined approach into practice is more straight-forward—discussing the receipt of age-appropriate vaccination or addressing issues such as pain or fatigue are daily aspects of a provider's routine clinical care. Other algorithms are more challenging to incorporate, perhaps due to lack of comfort with evolving science outside of our own field or lack of expertise in how to counsel patients on incorporation of emerging evidence into daily life. This lack of comfort around addressing issues outside of cancer highlights the difficulty in transitioning one's thinking from single-specialty focus to broader holistic clinical practice.

In 2015, we introduced an algorithm on anthracycline-induced cardiotoxicity to the NCCN Guidelines for Survivorship.[3] This algorithm addressed how to approach surveillance for survivors who had been treated with anthracyclines; it engendered a lot of lively discussion both within the panel and within our member institutions. The evidence suggests that the overall incidence of anthracycline-induced cardiotoxicity—defined as symptomatic heart failure—is less than 5% in most modern studies, but that a greater proportion of patients (10%–15%) may develop asymptomatic left ventricular dysfunction due to their anthracycline exposure.[4–7]

The field of cardiology has now defined 4 stages of heart failure, which includes the group of patients at risk for heart failure due to specific risk factors, such as exposure to cardiotoxic therapies (stage A), with management recommendations proposed for each stage.[8] Recent studies have shown the benefit of prospective identification and management of patients with asymptomatic left ventricular dysfunction or those at high risk (defined as having cardiovascular disease or high-risk factors such as diabetes), including lower rates of progression to symptomatic heart failure or heart failure–associated death.[9,10] However, these studies were not performed in patient populations that had received anthracycline treatment or those with cancer. Therefore, the oncology community is left without solid evidence on how best to interpret these findings within the context of managing a patient with cancer.

Evolving data also suggest that cardiovascular disease remains a major cause of non–cancer-related deaths in survivors; for example, cardiovascular disease ultimately exceeds the risk of breast cancer–related death at 9 years in studies of breast cancer survivors.[11,12] This may be due to long-term effects of cancer therapy–related toxicities

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(anthracyclines) as well as shared etiologies, including obesity, lack of physical activity, and less than optimal dietary habits.[13] Population-based cohort studies of patients with breast cancer treated with chemotherapy suggest an increased risk of cardiac dysfunction when compared with age-matched controls without cancer, with the greatest risk seen in those who receive trastuzumab sequentially with chemotherapy. However, minimal excess risk was seen with anthracycline exposure alone.[14] Studies have also suggested that the risk for cardiac dysfunction is greatest in the first year after treatment and may be somewhat reversible with timely intervention and standard heart failure management.[15] Although small studies have suggested a protective role for β-blockers or angiotensin-converting enzyme inhibitors in preventing anthracycline-induced cardiac dysfunction, not all studies have demonstrated benefit, nor has a single approach been identified as "best practice."[16] A number of clinical trials are ongoing (www.ClinicalTrials.gov), but have yet to solidify best practices for surveillance or provide definitive evidence supporting the role of these agents in either prevention or treatment.

In turn, the Antharcycline-Induced Cardiotoxicity algorithm was developed to address the evolving data and changing landscape in the fields of oncology and cardiology. Developed by a subcommittee that included representatives from the fields of cardio-oncology and medical oncology, this algorithm recommended that providers categorize anthracycline-treated patients as having at least stage A heart failure (defined by the American College of Cardiology/American Heart Association as being at risk for heart failure due to exposure to potentially cardiotoxic chemotherapy and no structural cardiac abnormalities); specifically, the algorithm encourages both the active management of concurrent cardiovascular disease risk factors and screening for cardiac dysfunction with a posttreatment echocardiogram within 1 year of completing therapy.

These recommendations are clearly a transition in thinking for oncologists, who may not view the incidence of anthracycline-induced cardiotoxicity as being excessively high, or may not uniformly address cardiovascular disease prevention recommendations with survivors. The recommendations also required a transition in thinking for cardiology colleagues, who expressed a strong belief that anthracycline-induced cardiotoxicity was a significant problem that should be screened for in every anthracycline-treated survivor and managed per general heart failure guidelines. With no category 1 evidence to guide us in this specific survivor population, the algorithm was vetted through the subcommittee, the larger NCCN Guidelines Panel, and all NCCN Member Institutions. Both cardiology and oncology input was strong and rooted in individual evidence base, each correct in their own position based on the available data. The final product was published last year, a work of compromise and collaboration based on rigorous evaluation of available evidence and expert input across both specialties.

To compliment these new recommendations, the Healthy Lifestyles algorithm was revised to be more inclusive of issues such as weight management, nutrition, and supplement use.[3] These recommendations may seem like "no-brainers," but data suggest that providers rarely discuss issues related to healthy lifestyles during survivorship visits.[17,18] Although much less controversy arose in the development of recommendations for maintenance of a healthy weight, adoption of a healthy diet, and promotion of routine physical activity, the panel had to consider not only which recommendations to make but also how to operationalize these recommendations at the individual provider level. Most providers do not have an extensive background in nutritional counseling, weight management, supplement use, or exercise physiology, and our challenge in developing the algorithm was to ensure that enough information was provided to the practitioner so that he or she could counsel survivors effectively regarding healthy lifestyle improvement. The challenge of operationalizing

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management recommendations within the context of an oncology-oriented clinic visit is not far from the panel's mind; we ultimately streamlined many of the algorithms by striking an appropriate balance between reflecting best practices in the field while considering the time and expertise of a busy provider.

The challenge in developing survivorship guidelines, with management recommendations that may be relatively foreign to oncologists, is to integrate recommendations based on existing evidence and best practices from all appropriate fields of medicine in a way that can be efficiently operationalized during a busy clinic visit. For many of the algorithms, the recommendations are based on a combination of evidence from populations without cancer, small studies of cancer survivors, other professional organizations' guidelines, and consensus expertise, because few large randomized trials are available on which to base recommendations. We endorse referrals to other providers with the expertise necessary to address a given issue, but the panel also wants to provide guidance for providers in situations where resources may not be so accessible.

To best improve survivorship outcomes and management algorithms, the oncology community must invest in research on ways to prevent, risk-stratify, and address late and long-term effects. We must learn from ongoing and past studies of healthy lifestyle interventions to identify the best methods to improve survivors' health. We must critically evaluate guidelines and management algorithms that are used in populations without cancer to determine whether it would be appropriate to apply these to a survivor population or whether specific variables or covariates may impact the management of a population of patients with cancer and may need to be further evaluated in an independent setting. Until those studies are complete, we must be willing to change our thinking and broaden our views so that we can incorporate the best evidence available from other specialties, transitioning from an oncology-oriented mindset to a more integrated multidisciplinary patient health management approach.

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