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VIEWPOINT

Clinical Practice Guidelines in Cardio-Oncology

A Sea of Opportunity

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
– Goethe[1]

Finding safe and effective treatments to improve patient outcomes is the holy grail of medicine. As defined by the Institute of Medicine (IOM), clinical practice guidelines (CPG) are statements that include recommendations intended to optimize patient care. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.[1] However, as the IOM has noted, evidence supporting CPG development relevant to subpopulations, such as patients with comorbidities and those with rare conditions, is usually absent. Therefore, many challenges exist in convening multidisciplinary guideline development groups to reconcile conflicting recommendations.

Recently, the European Society of Cardiology (ESC) published the much-anticipated cardio-oncology CPG in collaboration with the European Hematology Association, the European Society for Therapeutic Radiology and Oncology, and the International Cardio-Oncology Society (ICOS).[2] The ESC CPG aim to help all health care professionals provide care to oncology patients before, during, and after cancer treatment concerning their cardiovascular (CV) health and wellness. Furthermore, it provides guidance on the definitions, diagnosis, treatment, and prevention of cancer therapy-related cardiovascular toxicity (CTR-CVT) and the management of cardiovascular disease (CVD) caused directly or indirectly by cancer.

The authors and members of the ESC Task Force in Cardio-Oncology should be congratulated for their achievements. Evolved from the 2016 ESC Position Paper,[3] the ESC CPG comply with the recommendations for formulating and issuing ESC guidelines. The CPG Committee and subspecialty communities of the ESC made the CPG development processes transparent. The ESC regularly updates CPG, assesses adherence, and evaluates implementation levels using quality indicators. In addition, pocket guidelines, guideline apps, slide sets, and patient summaries are provided.[2] In other words, the quality criteria of the ESC are analogous to the IOM standards for trustworthy CPG[1] regarding the 8 components (transparency, conflict of interest, group composition, systematic review, evidence foundation, articulation of recommendations, external review, and updating). Thus, although CPG do not override the individual responsibility to consider patient-specific situations and country-specific regulations, health professionals are encouraged to consider the guidelines.[2]

As a first step, the new proposed definition of CTR-CVT and the personalized algorithms presented in the ESC CPG are a significant step forward. The predominant focus was cardiotoxicity when the National Institutes of Health discussed the need for greater evidence-based clinical guidance at the Workshop in 2013.[4] At that time, there was limited evidence in this multidisciplinary field because CV trials excluded patients with cancer comorbidity and vice versa.

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Therefore, the reconciliation of conflicting CPG was urgent between cardiology and oncology.[5] Since then, development of consensus recommendations and guidelines[4,6,7] have facilitated the mutual understanding of sharing common goals to optimize patient outcomes.[8] For example, the Common Terminology Criteria for Adverse Events revised standardized terminology for heart failure before the second National Institutes of Health Cardiotoxicity Workshop in 2018.[4] However, classifications of cancer therapy-related cardiac dysfunction (CTRCD) remain disparate.[6] Moreover, novel CV conditions associated with new cancer treatment modalities have emerged.[7] Thus, the new definition of CTR-CVT is one of the essential elements of the ESC CPG and represents the expanded and current scope of cardio-oncology.

The new management algorithms of the ESC CPG represent a paradigm shift from a drug-centric to a patient-centric approach. The absolute risk of CTR-CVT is essential for understanding and balancing the risks and benefits of cancer treatment. However, several variables can influence CTR-CVT risk. The recommendations of the ESC CPG are built on a very clear and logical premise that involves 5 steps: baseline risk assessment, surveillance during cancer treatment, management of CTR-CVT, end-of-cancer therapy assessment, and long-term survivorship strategies for high-risk cancer survivors, with approaches tailored to individual risk.

Although much progress has been accomplished since the ESC 2016, the authors of the ESC CPG are aware of the gaps in evidence and future needs for this first cardio-oncology CPG to be more relevant, feasible, and sustainable.

The relevance of recommendations needs to be understood in the context of the evidence supporting them. Rather than a "one-size-fits-all" approach, CPG can enhance clinician and patient decision making by clearly describing and appraising the scientific evidence and reasoning behind clinical recommendations.[1] In the ESC CPG, the classes of recommendation are high: Class 1 ("is recommended or is indicated") had 156 (57.4%) of 272; Class 2a ("should be considered") had 75 (27.6%) of 272; and Class 2b ("may be considered") had 36 (13.2%) of 272. However, the levels of evidence supporting these recommendations were not very high: Level of Evidence: A ("multiple randomized clinical trials or meta-analyses") had 7 (2.6%) of 272; Level of Evidence: B ("single randomized clinical trial or extensive nonrandomized studies") had 57 (21.0%) of 272; Level of Evidence: C ("consensus of the experts and small studies, retrospective studies, registries") had 208 (76.5%) of 272. In clinical domains in which high-quality evidence is lacking, guideline development should meet all 8 IOM standards for trustworthy CPG.[1] Therefore, compliance with the CPG quality criteria is important for the ESC CPG. In the future, new imaging modalities and biomarkers need to be developed and validated as better surrogate endpoints.[4] Moreover, new methodologies for clinical evaluations should be explored in the era of personalized medicine.[9] In the meantime, because CPG are used not only by physicians, but also by insurers, quality assessment organizations, and malpractice lawyers, there may be an imperative to prepare separate documents where evidence is limited.[8]

The feasibility of the new CPG poses another challenging question: are the new management algorithms are actionable? As the authors acknowledged, there are few dedicated cardio-oncology services available worldwide.[2] We must admit that Japan is no exception.[10] Thus, for shared decision making by health care providers without specialized cardio-oncology services, patients may wonder who will be responsible for the following 5 steps of their CTR-CVT risk evaluation and management.

As the first step, baseline CV risk assessments are recommended (Class 1, Level of Evidence: B) for all patients receiving potentially cardiotoxic anticancer therapy. These recommendations are for oncology teams to promptly optimize cancer treatment, personalize CTR-CVT strategies, and educate patients. In addition, to facilitate clinical uptake, the ESC CPG recommend using pretreatment risk assessment tools (Class 2a, Level of Evidence: C), including the one developed by the Heart Failure Association and ICOS. However, although the Heart Failure Association and ICOS tool covers 7 categories of cancer therapy, there are 18 categories in the ESC CPG, including baseline assessments for osimertinib (Class 1), radiotherapy (Class 2a), and stem cell transplantation (Class 1). Thus, challenges remain before complete clinical uptake by oncologists can be achieved.

The second step is preventing and monitoring CTR-CVT during cancer treatment. While this part is mainly for oncologists, it also introduces modern cancer therapies for cardiologists. Historically, there have been numerous controversies over the feasibility of cardio-oncology guidelines: either excessive or insufficient.[8] The new personalized approach aims to enable early detection of CTRCD and to reduce the burden on oncologists. Biomarkers and imaging will be helpful if validated. However, only 6 of 18 CTR-CVT algorithms use baseline risk categories. Also, recommendations on primary or secondary prevention are limited to anthracyclines and radiotherapies.

In Japan, evidence-based benefit-risk analyses are warranted because most CTR-CVT primary preventions are off-label.[10] Overall, while the risk-based approach makes CTRCD surveillance efficient, the new definition of CTR-CVT poses the need for evidence in prevention and monitoring.

The third step is the management of CTR-CVT, which is crucial for balancing the care of acute phase CVD and effective cancer treatment. This step is mainly for cardiologists but also introduces modern cardiology for oncologists. Based on the CPG for noncancer CVD, the ESC CPG highlight recommendations where CTR-CVT management differs due to cancer or cancer treatment. For example, anticoagulation for atrial fibrillation and venous thromboembolism differs in patients with cancer because they require an assessment of TBIP (thrombosis, bleeding, drug interaction, and patient preference). Notably, a new recommendation is to continue HER2 (human epidermal growth factor receptor 2)-targeted therapy with close CV monitoring when CTRCD is asymptomatic and moderate. This will save many patients from unnecessary discontinuation of effective cancer therapies. In addition, a detailed protocol for immune checkpoint inhibitor-related myocarditis will help prepare for rare but fatal CTR-CVT. Thus, this part is quite feasible for cardiologists who must support the completion of effective cancer therapies in understanding the overall benefit-risk analysis.

The fourth step, the end-of-cancer therapy CV risk assessment, identifies patients who benefit from education and support on modifiable CV risk factors. However, there are only a few dedicated cardio-oncology services available in Japan.[10] Therefore, oncologists should be encouraged to refer eligible patients to cardiologists.

The last step, the long-term follow-up for cancer survivors, is outlined as recommendations for pediatric and adult cancer survivors. In general, visits to oncologists decrease with time while CV events increase. Therefore, patients should receive guidance for a healthy lifestyle and how to identify symptoms of CVD, as well as psychological support for active CV risk management.

The sustainability of CPG relies on the ecosystem for regular updates. However, in cardio-oncology, rapid progress in both oncology and cardiology leads to not only new cancer therapies but also new heart failure management strategies, including angiotensin receptor-neprilysin inhibitors and sodium-glucose cotransporter 2 inhibitors, which are not yet mentioned in the ESC CPG, the most up-to-date CPG. The breadth of the scope and depth of the recommendations will be the balance between quality and speed. In Japan, guidance documents covering broad aspects of oncology cardiology were first published based on expert opinion. A more focused CPG based on a systematic review is currently being prepared.[10] Ideally, CPG and guidance documents should be prepared not because the evidence is available, but rather because the evidence is needed to address unmet medical needs. However, the voices of patients who unfortunately experienced CTR-CVT are often overlooked in part because of survivorship bias. Therefore, the IOM recommends public and patient involvement in the process of CPG development where evidence levels are limited.[1] In cardio-oncology, public and patient involvement will be the key to advocating for risk-based, data-driven decision making.

In summary, although this area of medicine has limited trials and evidence on which to base decision making, the ESC CPG has evolved from the 2016 ESC Position Paper with new definitions of CTR-CVT and personalized algorithms. However, as the authors describe, strategic investments in cardio-oncology care networks and cardio-oncology services are needed to make this interdisciplinary project relevant, feasible, and sustainable. Therefore, the new CPG are expected to serve as an invaluable foundation in the quest for safe and effective care in cardio-oncology—a sea of opportunity.

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