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## PATIENT ADVOCACY

# Enhancing quality of life as a goal for anticancer therapeutics

THE GLOBAL BIOMEDICAL COMMUNITY'S SUCCESSES IN CANCER THERAPY OVER THE past 30 years and particularly in the last 5 years have made many cancers survivable diseases (1). The U.S. National Academy of Medicine's 2013 Quality Cancer Care report estimates 18 million survivors in the United States by 2018 and 1.5 million new cancer diagnoses per year. The increase in treatment options and survival progress for many cancer types brings into sharper focus the responsibility to also prioritize continued improvements in the quality of life throughout disease-directed treatment and the full continuum of care for both cancer patients and survivors.

In the weeks, years, and decades after treatment, many survivors experience a significantly higher incidence of serious and even life-threatening chronic conditions—often unintended consequences of toxicities from the drugs and therapies that saved their lives (2). These consequences can include cardiac dysfunction or failure, pulmonary disease, neurological deficits, liver injury, and endocrine disorders. In addition to their physical and emotional toll, these effects interfere with daily functioning and quality of life, including overall well-being, ability to maintain employment, financial stability, and relationships with friends and family.

The most commonly cited example in this realm is the latent cardiotoxicity that can follow high-dose anthracycline therapy used to treat childhood leukemias and osteosarcomas. Indeed, survivors of childhood cancer have a sevenfold higher risk of cardiac mortality than the general population (3). However, such off-target toxicities are not limited to traditional cytotoxic or radiotherapies. As the use of targeted therapies (including immunotherapy) to treat previously refractory cancers expands, so does the evidence of adverse off-target effects from these drugs. A recent review highlights the diversity of immune-mediated toxicities resulting from anti-CTLA-4 and anti-PD-1 antibody therapies (4). Many of these effects are reversible with a halt in treatment, whereas other treatment-related effects require complete cessation of therapy because of their severity. In some instances, immune-mediated, potentially fatal hepatotoxicity and cytokine-release syndrome were observed with these treatments, and dose stoppage was the only option. Other treatment-related effects may be subtler but can nonetheless significantly compromise a patient's quality of life. For example, lingering cognitive- and executive-function deficits have been associated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) used to treat renal cell carcinoma (5).

Whether attempting to protect against slowly evolving cardiac damage or acutely manifesting cytokine storm, the translational science knowledge base required to inform clinician and patient decisions about dosing, protection, and monitoring is at best incomplete. Because of our limited mechanistic understanding of the onset and progression of these adverse effects of therapy, we lack diagnostic or predictive biomarkers of toxicity and have few protective co-therapies to mitigate adverse effects. These deficits limit the ability to personalize the effective dose for patients in need and have a negative impact on the quality of life for patients and survivors who have overcome so much already.

As advisory board members of HESI THRIVE (<http://hesithrive.org>)—a funding agency for quality-of-life research—we call on the biomedical and patient advocacy communities to join us in raising the visibility of this important yet under-resourced and under-recognized opportunity to improve the lives of cancer patients and survivors. The time is right to broaden our perspective on what it means to make more therapies available to more patients. Consider the fact that “toxicity” is one of only three elements of evaluation in the American Society of Clinical Oncology's 2015 conceptual framework to assess the value of cancer treatment options (6). And yet, despite its heavy emphasis on toxicity, the framework's authors note the limited data available for assessing the quality of life and chronic impact of these drugs. Thus, they subsequently rely exclusively on reports of high-grade acute adverse effects (including death) from clinical trials, neglecting toxicities that might be low-grade but chronic and have a greater impact on overall quality of life than a more serious but acute and rapidly resolving adverse event. Surely, a more nuanced data set on which to base important therapy judgements can be developed.

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The potential for experimental research to identify new safety biomarkers or dosing strategies for minimizing toxicities of oncology therapies as an essential expanded focus for quality-of-life research remains largely unrealized. We believe that, with resources and prioritization, researchers can make real progress in this space. The impact of mechanistic and translational studies on anthracyclines is a case in point. When use of the anthracycline doxorubicin as an antineoplastic agent was launched more than 40 years ago, it quickly became evident that cardiotoxicity would be dose limiting. Studies in Syrian golden hamsters and rhesus monkeys soon replicated the drug's acute arrhythmogenic effects and became the launching point for exploration of dexrazoxane as a potential protective inhibitor of these cardiotoxicities. Further work in a range of preclinical animal models and in vitro assays has identified monitorable serum biomarkers of doxorubicin-induced toxicities, elucidated the protective pharmacology of dexrazoxane (iron chelation and topoisomerase II inhibition), provided proof of concept for different dose-optimization strategies, and characterized the mechanism of latent doxorubicin-induced cardiotoxicity (accumulated mitochondrial damage). Cumulatively, these findings have yielded dramatic changes in clinical dosing practices for doxorubicin and spurred the use of protective therapies such as dexrazoxane to enhance antineoplastic efficacy while reducing both acute and delayed adverse effects (7).

Currently, the U.S. National Cancer Institute's Provocative Questions initiative (PQ 9 specifically) and innovative seed-funding programs such as the HESI-Pardee THRIVE Initiative are among a very few that provide much needed, albeit modest, research funding in this space. Efforts led by the International CardiOncology Society, THRIVE, Friends of Cancer Research, and others add further depth of field by creating new, multidisciplinary communities of practice to synergize expertise and applications. There is a growing network of expertise behind the prevention, prediction, and management of treatment-related toxicities that can limit patient adherence to treatment or a survivor's ability to thrive after treatment.

The need for, and the achievability of, a quality-of-life-driven research agenda has never been stronger. By increasing the rigor, visibility, and frequency of this research, we also increase the potential to both broaden the lifetime benefit of existing cancer treatments and enhance the reach of future therapies.

**–Syril D. Pettit, Steven E. Lipshultz, Charles S. Cleeland, Samantha Roberts, Myrtle Davis, Brian R. Berridge, Rebecca A. Kirch**

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