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EDITORIAL COMMENT

Overcoming Inertia to Tame the Red Devil*

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The incidence and prevalence of breast cancer is high globally, with 1 in 8 women expected to develop breast cancer in their lifetime (1-3). Treatment has changed significantly over the decades. The main advance in the treatment of early stage breast cancer was the integration of anthracyclines in the adjuvant treatment protocols in the early 1990s, resulting in a 10% improvement in disease-free survival (DFS) and a 7% improvement in overall survival, compared with the initial standard regimen of cyclophosphamide, methotrexate, and 5-fluorouracil (4). In the early 2000s, taxanes were developed, and their addition to an anthracycline regimen was found to boost DFS and OS even further (5). Since that time, despite the advent of other, newer agents, the anthracycline and taxane backbone has not been surpassed and remains a mainstay of treatment for breast cancer (6).

Anthracyclines exert their effect on cancer cells by several mechanisms, including inhibition of DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand, by creating iron-mediated free oxygen radicals, by damaging DNA and cell membranes, and by the inhibition of topoisomerase II (7). The efficacy of these agents in cancer therapy has resulted in their permanent and featured position in most regimens for breast cancer, lymphoma, and sarcomas. Their side effect profile has led anthracyclines to be dubbed the "red devil" by patients and oncology care providers, given their ability to cause nausea, vomiting, myelosuppression, and alopecia, as well as its rosy hue in the IV bag (8). The risk of cardiotoxicity with doxorubicin, both in the short term and in the long term, was found to be heavily dose dependent, and in early studies cardiotoxicity was realized to occur more readily when the cumulative dose exceeded 500 mg/m^2 (9). Limiting cumulative dose is an effective method of decreasing heart failure rates, but is not perfect, as cardiotoxicity is still observed in patients receiving less than recommended cumulative doses (10). This strategy, unfortunately, also limits the amount of this highly effective antineoplastic agent that can be delivered in an individuals' lifetime.

Dexrazoxane was developed in the 1980s and was approved by the Food and Drug Administration in 1995 for reducing the incidence and severity of cardiomyopathy associated with doxorubicin (11). While several mechanisms of action have been proposed, dexrazoxane is mainly thought to exert its effect by displacing iron from anthracyclines and preventing the formation of complexes between anthracycline and topoisomerase II beta (12). This allows for the administration of a greater cumulative doxorubicin dose and decreases the risk of heart failure, as reliably shown in multiple studies over the past several decades. As such, a simple solution was born. The uptake and use in clinic, however, have always seemed to lag behind.

Why was dexrazoxane not adopted more readily in clinical practice? Unfortunately, as a society we are much more likely to utilize a new treatment with slight improvement in efficacy than we are an older agent with strong evidence of its role in supportive care. It almost seems as though this is the opposite of a patient-centered approach, but we tell ourselves it is not. As with the adoption of any new medication, important skepticisms need to be addressed to ensure safety. Specifically: Will it work well? Will this

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agent result in further side effects for the patient to endure? Will it compromise the efficacy of the anticancer medication? In the early studies of dexrazoxane, these outcomes were measured carefully. With regard to increased toxicity, it was noted that there were increases in hematologic toxicities in patients receiving anthracyclines and dexrazoxane, but no additional dose delays or reductions (13). In pediatric patients, concern was raised about the potential increase in risk of second malignant neoplasms, on the basis of a randomized study of 478 patients with Hodgkin's disease (14), but this was later refuted with larger, longer term studies demonstrating no such increase in risk (15). While no individual study identified decreased efficacy of the antineoplastic agents, a meta-analysis in 2005 noted a nonsignificant trend toward lower response rates in those patients treated with anthracyclines in combination with dexrazoxane versus those patients assigned to anthracyclines alone (relative risk: 0.88; 95% confidence interval: 0.77 to 1.01; $p = 0.06$) (16). Due in large part to this single nonstatistically significant trend, American Society of Clinical Oncology guidelines were published in 2002 and updated in 2008 to reflect that in the setting of adjuvant breast cancer, dexrazoxane should not be added to adjuvant therapy and should be considered in the metastatic cancer setting only if the dose of doxorubicin exceeds 300 mg/m^2 and the patient is still obtaining clinical benefit (17). This was quite a strong position to take, given that none of the systematic reviews completed had evaluated the effect of dexrazoxane exclusively in breast cancer patients treated with anthracyclines. In addition, as one of the main guideline organizations oncologists turn to for advice, this staunch position taken to directly state that this agent should not be used is a tough hill to climb and overcome. This is likely why dexrazoxane has not received a warm welcome in the oncology clinics, but more a curious interest by positive deviants in settings where doses of anthracyclines need to exceed into the cardiotoxic ranges. Certainly, the most attention dexrazoxane has had of late seems to be in relation to notifications of worldwide drug shortages. The overall message to oncologists seems to be that this is an agent that could be considered, but cautiously and sparingly.

Currently, the long-term noncancer issues facing breast cancer survivors are becoming increasingly important. Thanks to improvements in surgery, radiation, and systemic therapy, a woman diagnosed with breast cancer now has 5-year DFS rates in the range of 90% to 95% (18). We are now in an era, thankfully, where a patient's long-term risk of other health issues outweighs the risk of cancer recurrence. Several studies have shown that the risk of development of cardiovascular disease in a woman with a prior diagnosis of breast cancer is much higher than in women who were never diagnosed with breast cancer. This risk varies according to baseline cardiovascular risk factors and type of treatment received, but overall estimates are 1.77 times higher for women with breast cancer than for non-breast cancer age- and cohort time enrollment-matched controls (19). Similar studies in the United Kingdom also demonstrated higher than expected rates of future cardiovascular disease in breast cancer survivors (20). Yet, we still are heavily focused on cancer treatment and may have trouble paying attention to future risk prevention strategies.

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In this issue of *JACC: CardioOncology*, Macedo et al. (21) have attempted to cut out the noise seen in other meta-analyses of dexrazoxane in prevention of anthracycline cardiotoxicity, by focusing exclusively on breast cancer patients receiving anthracyclines. In doing this, these investigators have managed to extract data from 2,177 patients and have found a significant reduction in the risk of congestive heart failure and cardiac events (relative risk: 0.19 and 0.36, respectively) with the use of dexrazoxane (21). While other meta-analyses demonstrated that dexrazoxane was effective, this most recent body of work provides the magnitude of benefit that can be appreciated by our patients with breast cancer specifically. What is unique to this study is the ability to demonstrate that the use of dexrazoxane was, in fact, not associated with detrimental effects on the response rates, overall survival, or DFS in patients with breast cancer. Indeed, there was a nonstatistically significant trend in improvement in progression-free survival noted in this meta-analysis, perhaps due to the ability to continue to deliver such an effective drug safely (21).

How does this compare with other strategies used to decrease the cardiotoxicity of anthracyclines? Beta-blockers and angiotensin-converting enzyme inhibitors have also been shown to be effective, likewise, at mitigating the future risk of heart disease in breast cancer survivors, especially those taking trastuzumab (22). However, the issue with these agents is how long must they be administered? When should they be started, and when should they be stopped? Other formulations of doxorubicin have also been developed as well in an attempt to mitigate the issues of cardiotoxicity. Liposomal doxorubicin is one such formulation, and some guidelines suggest that this agent can also be considered in certain clinical situations (23). Similarly, exercise programs have

been shown to play an important role in prevention and rehabilitation of cardiotoxicity in cancer patients (24). The dose, frequency, and type likely needs to be adapted to each individual patient, and compliance is the main issue with this modality. Although these strategies have not been directly compared head to head, given the data currently available, it would seem that dexrazoxane is one of the most effective and reproducible methods of taming the red devil.

Dexrazoxane has a role, but the question that remains is which patients with breast cancer truly are in need of this protective agent? The studies summarized in this most recent meta-analysis have used quite a wide range of doses of anthracyclines, as well as a wide range of disease stages—from very early and highly curable to overtly metastatic and incurable (21). We also do not have the ability to tease out the baseline cardiovascular risk for the individuals included in this study, which may also factor heavily into predicting those who would appreciate the most gain from such a cardioprotectant. Wouldn't it be great if we could derive a test or a nomogram with reliable likelihood ratios to predict future risk of anthracycline cardiotoxicity for patients with breast cancer? Work is being done to identity genetic tests that can help predict risk in pediatric patients receiving anthracyclines (25). Long-term observational studies such as the Childhood Cancer Survivor Study have identified clinical factors associated with higher risk of subsequent heart failure in pediatric patients (26). Lifestyle factors, comorbidities, cumulative dose, and breast cancer risk would all need to be factored to develop such a prediction tool, but this would likely require prospective observation over a long period to answer properly. Macedo et al. (21) suggest a randomized clinical trial to further elucidate the nuances of dexrazoxane benefit in breast cancer patients. Careful thought, planning, and collaboration are needed to study this issue in a contemporarily meaningful way.

As with many preventive strategies in medicine, the inertia of adopting a new treatment is victim to the competing motivations of oncologists, patients, and cardiologists at the time of initial consultation. We know that there are risks, but they seem a long way off in the moment when an immediate life-threatening illness is faced. For the time being, is there harm in adopting its use more widely? This meta-analysis would suggest not, and that we should take a step forward towards taming the red devil, and focus more steadily on saving hearts while curing cancer.

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