Since their first discovery nearly 50 years ago, anthracyclines, including doxorubicin (Adriamycin), daunorubicin (Cerubidine), epirubicin (Ellence), and idarubicin (Idamycin PFS), have been successfully developed as potent anticancer therapeutics with significant efficacy in lymphomas and many solid tumors. Particularly in patients with breast cancer, they are the primary choices of therapy. However, cardiotoxicity has been a central limiting complication in treating patients because the agents acutely produce arrhythmias, left ventricular dysfunction, and pericarditis and chronically lead to left ventricular dysfunction and heart failure. The toxicity is clearly dose related, with sharp rises in left ventricular dysfunction with cumulative doses >400 to 450 mg/m² for doxorubicin. When cardiac imaging was used, the incidence of heart failure was 5%, 26%, and 48% in patients receiving 400, 550, and 700 mg/m² doxorubicin. As a result, most oncologists typically limit the dose to 450 to 500 mg/m². Children are especially vulnerable, with rates of significant left ventricular dysfunction of 5% at 15 years of follow-up, increasing to 10% for cumulative doses of ≥550 mg/m². Heart failure may present many years after treatment. Mediastinal irradiation is an additional risk factor that may also be particularly problematic in children. To date, our only proven protective measure is adherence to stopping guidelines for total dose. Unfortunately, this typically limits the total dose an individual patient could receive, and for particularly problematic cancers, oncologists would like to use higher doses.

This issue may be particularly problematic in patients with breast cancer who are positive for human epidermal growth factor receptor 2. This receptor is amplified in ≈breast cancer who are positive for human epidermal growth factor receptor 2 monoclonal antibody trastuzumab (Herceptin). This finding also breathes interesting new life affecting its anticancer efficacy. It is indeed remarkable and exciting that novel and possibly game-changing approaches to protect cardiomyocytes against doxorubicin treatment without affecting its anticancer efficacy. It is indeed remarkable and exciting that novel and possibly game-changing approaches to protect cardiomyocytes against doxorubicin treatment without affecting its anticancer efficacy.

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against doxorubicin treatment. Indeed, after so many years of clinical observation, revealing the functional role of topoisomerase-IIβ in doxorubicin-mediated cardiac injury might offer a bona fide mechanism for the beneficial effect of dexrazoxane. Largely because of that, another trial in the clinic with dexrazoxane or similar compounds is likely.

The report in this issue of Circulation from the Lee laboratory offered another novel approach to achieve biased protection in cardiomyocytes against doxorubicin treatment. Neuregulin-1β functions through its receptors, ErbB2 and ErbB4, to exert potent cardioprotection against doxorubicin-induced injury. However, it can also induce oncogenic activity through receptor-mediated signaling in cancer cells. This poses an especially critical dilemma for breast cancer patients, even with staged doxorubicin/trastuzumab therapy. Interestingly, ErbB4 is enriched in cardiomyocytes and can transduce protective signaling through homodimer interaction, whereas cancer cells express ErbB3, which requires ErbB3/ErbB2 heterodimer interaction to transduce downstream oncogenic effects. Jay et al from the Lee laboratory exploited this property using a modified neuregulin-1β ligand. By tethering 2 molecules with a linker, this bivalent neuregulin-1β ligand (NN) has a strong preference for homodimer signaling over heterodimer signaling in the target cells.

Both in vitro and in vivo, the newly engineered NN showed a potent cardioprotective effect against doxorubicin treatment (where ErbB4 homodimers signal downstream to prosurvival pathways) and demonstrated significantly reduced progrowth signaling and proneoplastic potential in cancer cells (where ErbB4 homodimers fail to signal to downstream pathways). Despite these exciting advancements, clinical translation of these newly established cardioprotective strategies needs to be further validated. Both studies showed potent protective effects to attenuate doxorubicin-induced cardiomyopathy in mice but did not provide in vivo evidence of preserving anticancer potency in an animal model. Because doxorubicin-induced cardiomyopathy can develop many years after treatment, longer-term observation will also be critical. Nevertheless, these 2 reports represent significant advances in our current therapeutic approaches to anthracycline-induced cardiomyopathy. They also highlight the importance of a better understanding of the disease processes and the therapeutic agents at a mechanistic and fundamental level to achieve rational design of therapies. These 2 successes demonstrate again that mechanism-based engineering (genetic or protein) holds great promise to tackle complex and challenging diseases in addition to cardiotoxicity of cancer therapies.

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References


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Mechanism-Based Engineering Against Anthracycline Cardiotoxicity
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