Since their first discovery nearly 50 years ago,\textsuperscript{1} 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 heart failure.\textsuperscript{2} The toxicity is clearly dose related, with sharp rises in left ventricular dysfunction with cumulative doses >400 to 450 mg/m\textsuperscript{2} for doxorubicin.\textsuperscript{3} When cardiac imaging was used, the incidence of heart failure was 5%, 26%, and 48% in patients receiving 400, 550, and 700 mg/m\textsuperscript{2} doxorubicin. As a result, most oncologists typically limit the dose to 450 to 500 mg/m\textsuperscript{2}. 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/m\textsuperscript{2}.\textsuperscript{4} Heart failure may present many years after treatment. Mediastinal irradiation is an additional risk factor that may also be particularly problematic in children.\textsuperscript{5} 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 ≈30% of breast cancers, leading to activation of signaling pathways that promote proliferation of the tumor cells and block tumor cell death.\textsuperscript{6} Initial strategies for treatment included concurrent anthracycline and the anti–human epidermal growth factor receptor 2 monoclonal antibody trastuzumab (Herceptin). However this led to a high incidence of cardiotoxicity.

Trastuzumab is now administered after completion of anthracycline dosing and has reduced the incidence of heart failure.\textsuperscript{7,8} Despite all of the above machinations to reduce cardiotoxicity of anthracyclines and trastuzumab, this problem remains a thorn in the side of the oncologist and cardiologist. Clearly, strategies to limit cardiotoxicity while maintaining anticancer efficacy are desperately needed.

Earlier studies have uncovered a number of mechanisms involved in anthracycline-induced cardiac injury.\textsuperscript{9,10} The most extensively characterized mechanism is anthracycline-induced reactive oxygen species and subsequent oxidative stress–induced DNA damage, mitochondrial dysfunction, sarcomere damage, and loss of prosurvival signaling. Unfortunately, numerous approaches focusing on the use of antioxidants were generally ineffective, at least in part because reactive oxygen species–induced cytotoxicity is a shared mechanism for both cardiotoxicity and tumoroidal activity. Consequently, our history of identifying novel strategies to prevent cardiotoxicity while preserving anticancer efficacy has a very checked past with few (or no) true successes.\textsuperscript{11}

However, recent findings from the Yeh laboratory\textsuperscript{12} and findings from the Lee laboratory\textsuperscript{13} reported in this issue of \textit{Circulation} offered 2 novel approaches to treat or prevent doxorubicin-induced cardiomyopathy (Figure). Although starting from very different vantage points, both laboratories exploited the subtle but important molecular differences between cardiomyocytes and cancer cells. In both cases, these differences were used as the mechanistic basis to develop strategies 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 an age-old conundrum (anthracycline-induced cardiotoxicity) were identified within a few months of one another.

In the report by Zhang et al.,\textsuperscript{12} a critical role of topoisomerase-IIβ in anthracycline cardiotoxicity was discovered on the basis of studies in both cultured cells and intact animals. They demonstrated that doxorubicin-mediated DNA damage and subsequent mitochondrial defects were topoisomerase-IIβ–dependent processes in cardiomyocytes. Doxorubicin-induced genomic DNA strand breaks, mitochondrial loss, cardiomyocyte death, and eventual left ventricular dysfunction were markedly reduced in topoisomerase-IIβ–knockout mice. Because topoisomerase-IIβ is selectively expressed in heart but topoisomerase-IIα is absent, a β isoform–specific inhibition of topoisomerase-II may offer a novel strategy to prevent doxorubicin induced cardiotoxicity without affecting its anticancer activities if topoisomerase-IIα remains functional in cancer cells. This finding also breathes interesting new life into an age-old debate over whether and how dextrazoxane, an iron chelator and topoisomerase inhibitor, is cardioprotective.
against doxorubicin treatment.\textsuperscript{14,15} Indeed, after so many years of clinical observation, revealing the functional role of topoisomerase-II\beta 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.\textsuperscript{13} Neuregulin-1\beta functions through its receptors, ErbB2 and ErbB4, to exert potent cardioprotection\textsuperscript{16} against doxorubicin-induced injury.\textsuperscript{17} 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\textsuperscript{18} from the Lee laboratory exploited this property using a modified neuregulin-1\beta ligand. By tethering 2 molecules with a linker, this bivalent neuregulin-1\beta ligand (NN) has a strong preference for homodimer signaling over heterodimer signaling in the target cells.\textsuperscript{18} 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).\textsuperscript{13}

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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