Editorial

Is There More for Us to Learn From Oncology?
Examining the Implications of Anthracycline Effects on the Young Heart

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Decades of basic and clinical research have improved the cure rates of many forms of cancer, particularly childhood malignancies. An unintended consequence of this success is the fact that cancer survivors are often left with increased risk of cardiovascular disease, particularly congestive heart failure, after the use of anthracycline antibiotic chemotherapeutics. Discovered 50 years ago, these agents have enjoyed widespread use in solid and hematologic malignancies for 30 years. The cardiac effects of these drugs remain a dose-limiting toxicity and can be neither predicted nor prevented. Oncology has adapted by reducing the total dose to limit exposure and developing cotreatments that reduce cardiac damage. This well-documented problem, which continues to induce cardiac dysfunction severe enough to warrant heart transplantation, is tolerated in part because of the efficacy of anthracyclines as important components of chemotherapy regimens. Studies examining possible mechanisms for anthracycline cardiac toxicity have been occurring for decades and have revealed many aspects of cardiac biology. Despite these efforts, there is no generally accepted mechanism for how these drugs cause heart failure.

A general construct for anthracycline-induced cardiac toxicity is that some form of cardiac injury occurs with every exposure. Compensatory changes at the cellular and subcellular levels allow recovery, permitting function to return to “normal” under resting conditions. Exercise stress–induced cardiac reserve is abnormal after anthracycline exposure, even when resting function appears normal. This conceptual view is further supported by the finding that persons at greatest risk are those with limited reserve such as patients with hypertension and old age. Thus, anthracycline exposure leads to a subclinical cardiomyopathy that manifests itself variably, depending on a number of factors, including total anthracycline dose and reserve.

A puzzle from this perspective is why children, who perhaps have the greatest cardiac reserve, are also at high risk for anthracycline-induced congestive heart failure. The explanation has been that the exposure to anthracyclines limits normal cardiac growth and therefore leaves the heart with chronically increased hemodynamic stress. This explanation is supported by echocardiographic studies of children exposed to anthracyclines showing that there is a reduction in ventricular wall thickness compared with age-matched children without anthracycline exposure that results in increased end-systolic wall stress.

An elevation in serum cardiac troponin over the course of anthracycline exposure suggests that a loss of myocytes occurs in children exposed to anthracyclines, which likely contributes to the decreased ventricular mass. Indeed, myocyte loss by a number of mechanisms can be demonstrated in isolated myocytes exposed to anthracyclines in vitro. However, recent studies have demonstrated that the young heart has a greater capacity for myocyte division and perhaps regenerative capacity. Should this enhanced regenerative capacity of the young heart not allow for better recovery from the anthracycline exposure?

De Angelis and colleagues provided a possible explanation to this conundrum in a recent study published in Circulation, showing that anthracyclines markedly diminish the number of cardiac progenitor cells. A potential flaw with that study was the use of an anthracycline dosing schedule that resulted in early cardiac dysfunction and high mortality that is very dissimilar to what is used clinically. In addition, this study did not specifically address whether this result occurs in young rodents. In this issue of Circulation, Huang et al have extended this observation further, demonstrating that anthracyclines induce a loss of cardiac progenitor cells in young mice at doses of anthracyclines that might be considered very dissimilar to what is used clinically. In addition, this study resulted in early cardiac dysfunction and high mortality that is very dissimilar to what is used clinically. They exposed young “juvenile” mice to repeated low doses of the anthracycline doxorubicin and found that the number of c-kit+ cardiac progenitor cells decreased in hearts after anthracycline exposure. In both in vivo and isolated c-kit+ cells, Huang et al go on to show evidence for “aging” with increased expression of the cell-cycle repressor p16INK4a and reduced telomerase activity. They demonstrate that the hearts of these mice are left with permanently altered vascular architecture with a quantifiable rarefaction of arteriolar branching and reduced capillary density.

Huang et al also show that anthracycline exposure impairs the ability of the heart to respond to stress. This is demonstrated with both pathological and physiological stress. In response to subsequent ischemic injury by surgical myocardial infarction, mice develop rapid heart failure. In response to swim training, in which mice with cardiac hypertrophy normally show improved diastolic function, there is no improvement. The authors conclude that the reduced number

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Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIR.0b013e3181d2e996
and accelerated senescence of progenitor cells set the heart up for the subsequent response to stress.

It is interesting to compare the population of cells studied by Huang et al with other populations that have emerged since the discovery of cardiac and other organ progenitor cell populations. Circulating CD34+ endothelial progenitor cells are increased in response to anthracycline exposure, at least in adult breast cancer patients. The mechanism for and clinical consequences of this, as well as how this finding relates to the current findings of Huang et al, warrant further investigation. Also interesting is the so-called side population of cardiac resident progenitor cells, which are defined and dependent on their ability to exclude organic anions because of the expression of ≥1 ATP-binding cassette transporters. Given that anthracyclines are a substrate for these same transporters, one might speculate that these cells have some resistance to anthracycline exposure.

Heart growth, like growth of other organs, is a carefully orchestrated change in tissue mass that balances hypertrophy of individual myocytes with microvascular and macrovascular growth. The impaired vascular anatomy induced by anthracycline treatment appears to leave the heart with impaired paracrine reserve. This is similar to studies examining the effects of antiangiogenic molecular strategies such as when angiogenesis of the heart is specifically suppressed by adenoviral overexpression of soluble vascular endothelial growth factor receptor. The result is reduced capillary density and impaired reactive hypertrophy in response to pressure overload. Perhaps a central problem created by anthracycline exposure is a limitation in the ability of the cardiac tissue to mount the appropriate paracrine signal necessary to orchestrate the coordinated growth/adaptation of the heart to the subsequent strain. Indeed, Huang et al found reduced vascular endothelial growth factor expression in the anthracycline-treated hearts. This appears to be a property of anthracyclines in other tissues; anthracycline treatment in tumor reduced the transcription of multiple HIF-1 target genes, including vascular endothelial growth factor. It will be interesting to learn what other factors involved in regulating cardiac growth are altered after anthracycline exposure. Many aspects of anthracycline toxicity warrant further investigation in the context of the findings of Huang et al. Anthracycline-induced DNA damage was not specifically examined by Huang et al but is likely at the heart of the observed accelerated senescence in progenitor cells. DNA, lipids, and proteins are susceptible to the oxidative stress induced by anthracyclines, particular as a result of iron-catalyzed Fenton chemistry. This has led to the development of the iron chelator dexrazoxane, which appears to prevent cardiac dysfunction associated with anthracyclines. It will be interesting to see whether dexrazoxane also prevents this cardiac progenitor cell injury and senescence.

It remains unclear what the “cardio-oncology” research community should do in response to these findings. Attempting to rescue the effect of anthracyclines on progenitor cell populations and the process of angiogenesis, as suggested by Huang et al, is unlikely to serve the interest of successful treatment of the cancer. In their study, De Angelis et al demonstrated that reinfusion of cardiac progenitor cells after anthracycline exposure provides some degree of cardiac rescue. However, it seems quite likely that such approaches will also prevent some of the beneficial effects of these chemotherapeutics on their targeted malignancies. Huang et al and De Angelis et al focused their attention completely on the heart. It would be interesting to know if the same progenitor cell senescence and vascular rarefaction that were observed in the hearts are also seen in tumors and other tissues that are a source of late complications of cancer therapy. Perhaps similar pathology might also be at play in other chronic health problems such as joint disease, cognitive dysfunction, and renal insufficiency incurred by cancer survivors.

An interesting biological aspect of the work by Huang et al, beyond the specific clinical problem under investigation, is the finding that anthracycline exposure “reprogrammed” the vascular-myocyte coupling that determines the “optimal” relationship between these tissues during changes in cardiac function. Long after anthracycline exposure, this remains disrupted. Understanding how and why this occurs may provide new insights into the regulators and mechanisms involved in this cell-cell interaction. It is tempting to speculate that this likely involves anthracycline-induced changes in mitochondrial function, oxygen sensing, and perhaps epigenetic adaptation to anthracycline-induced DNA damage.

From a clinical viewpoint, it is also intriguing to consider the possible therapeutic implications of the cardiac biology revealed by the oncology experiment by Huang et al. Some might consider it heresy to propose that the cardiotoxic effects of anthracyclines and their ability to ablate cardiovascular stem cells can be put to good use in the cardiology clinic. However, we should consider some inherited cardiomyopathies in which cardiac hypertrophy goes unchecked, particularly during youth, with high morbidity and mortality for which evolving treatments include ablation of septal myocardium by infusion of alcohol delivered selectively down a coronary artery. Perhaps it is worth examining whether anthracycline (or other cancer therapy) exposure at a critical dose, time, and place (selective versus general infusion) would limit the cardiac hypertrophy more permanently than current therapies. What about the more general problem of atrial fibrillation? As atrial fibrillation is in part a function of cellular plasticity in the pulmonary vein and recovery of atrial fibrillation after ablation is due in part to regeneration of myocardial electric connections, then perhaps chemotheraphy as a adjuvant to the current treatments using catheters and scalpels ought to be explored as a possible therapy. Needless to say, if we pursue this route, it will be important to keep our oncology colleagues close at hand.

Disclosures
None.

References


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Circulation. 2010;121:623-625; originally published online January 25, 2010;
doi: 10.1161/CIR.0b013e3181d2e996
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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