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Commentary

Enhanced Cardiac Testing in a Dual Anti-HER2 Regimen: What Have We Learned?

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Disclosures of potential conflicts of interest may be found at the end of this article.

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Concerns that cancer treatment caused cardiac dysfunction came to the forefront after the discovery of the anthracyclines in the 1960s. Damage to the heart subsequent to the administration of anthracyclines was dramatic, devastating, and sometimes fatal. While oncologists had tackled the adverse events of preanthracycline chemotherapy, the new phenomenon of anthracycline-associated cardiotoxicity created new challenges [1]. Through collaboration with cardiologists, those treating patients with cancer came to learn about this new mechanism of cardiac injury, and cardio-oncology was born.

Anthracycline toxicity was related to the cumulative dose, and an extensive database of endomyocardial biopsies demonstrated that myocyte death followed exposure to this class of agents when administered above a threshold dose that varied considerably among patients. Higher cumulative doses resulted in higher biopsy specimen grades, indicating increased cellular injury and a greater loss of myocytes [2].

Many questions had yet to be answered: Why did patients seem to do well from the cardiac standpoint after treatment, only to develop heart failure years or even decades after treatment? What were the risk factors that made heart failure more likely, and could cardiotoxicity be prevented or mitigated? We learned that the myocyte injury and cell death associated with anthracyclines took place in the days and weeks following administration. The damaged cells either recovered or underwent apoptosis, and the patient then went on with life, albeit with a heart that was not normal. When compensation was no longer complete, we saw the effects on various noninvasive parameters, the most enduring of which was a reduction in the left ventricular ejection fraction. Although countless coexisting conditions were identified as risk factors, they were ultimately summed up as any factor that had previously damaged the heart or any factor that made the heart more susceptible to future injury [3]. Finally, in addition to reducing the overall exposure to anthracyclines by dose reduction, chemical protection with dexrazoxane [4], lowering the peak plasma level by prolonged infusion schedules [5], and, albeit less convincingly, molecular or delivery system modification [6] all demonstrated significant but varying degrees of cardioprotection.

More recently it was found that biomarkers, especially troponins, were a good substitute for cardiac biopsy specimens in assessing actual myocyte destruction, and that reducing myocardial stress through β-adrenergic blockade and afterload reduction protected the heart. These agents appear to do so both during the phase of actual damage as well as during the period of posttreatment remodeling [7].

Newer targeted therapies, including monoclonal antibodies and tyrosine-kinase inhibitors, were not expected to cause cardiotoxicity, but when the pivotal trial that dosed trastuzumab along with doxorubicin suggested levels of cardiotoxicity far beyond those expected from the anthracycline alone, interest in the effects of cancer treatment on the heart exploded [8]. The rate of cardiac adverse events, initially reported to be 27%, has been cited extensively, although, fortunately, this level of cardiotoxicity has not been replicated. The subsequent series of clinical trials were conducted to establish both the efficacy of trastuzumab in the adjuvant setting and to determine the incremental extent of cardiotoxicity if trastuzumab was administered sequentially rather than concomitantly with an anthracycline.

When these trials were initiated, it had not yet been recognized that cardiac dysfunction seen with trastuzumab was quite different, both mechanistically and with regard to long-term implications, from the cardiotoxicity associated with anthracyclines and their inherent myocyte damage. Extensive monitoring was therefore incorporated into these trials. For better or worse, the exhaustive monitoring schemes used in these early trials were incorporated in clinical use, resulting in monitoring guidelines based more on clinical trial design than on the robust clinical insight that the trials provided. We continue to hear that cardiac monitoring of left ventricular ejection fraction should be undertaken every 3 months, despite the now widely recognized differences among potentially cardiotoxic agents. Agents that destroy myocytes (type I agents) may warrant intensive monitoring, especially for high-risk patients, but, as pointed out in the study by Yu et al. [9], this is probably not nearly as important for agents for which myocyte apoptosis is not part of their primary toxicity spectrum [10].

What was not initially explained was why the incidence of cardiotoxicity was so high in the pivotal trial or why patients who experienced cardiac events with trastuzumab usually, but not always, recovered. Why was it possible to continue trastuzumab (along with several other agents associated with cardiac events)

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for long periods of time—in some instances for longer than 10 years—with stable cardiac parameters in most of the patients so treated?

Explaining what was happening when trastuzumab and anthracyclines were given together involved a bit of detective work. Initially it was shown that trastuzumab interfered with cell repair [11]. Putting that bit of information together with the fact that when we repeated cardiac biopsies in patients previously treated with anthracyclines and in whom biopsy specimen evidence of toxicity was anticipated, no abnormalities were observed if an interval of 4–6 months had transpired since the last anthracycline administration. The assumption, albeit unproven, was that damaged myocytes either recovered and appeared normal in biopsy specimens, or had undergone apoptosis and were replaced in the cardiac matrix. Further evidence was provided by looking at the extent of cardiac events in the various trials—high in the pivotal trial when the agents were given together, much less when there was a 3-week interval between the last anthracycline dose and trastuzumab, and almost no events in the Herceptin Adjuvant (HERA) trial, in which the interval between anthracycline and trastuzumab was 89 days [12]. Could it be that what we were seeing was predominantly an augmentation of anthracycline toxicity induced by trastuzumab's inhibition of cell repair? This might also explain why so many patients have tolerated the drug for long periods of time after completion of anthracyclines.

While the oncologic efficacy of trastuzumab was clear from the start, the idea of adding a second anti-HER2 agent was intriguing, and this was the basis for the CLEOPATRA trial [13]. If the observed cardiotoxicity of trastuzumab was truly a secondary phenomenon because of its effect on cell repair, and if pertuzumab was not inherently cardiotoxic, then very little toxicity would be expected. Indeed, CLEOPATRA demonstrated the cardiac safety of the combined regimen [14], and Yu et al. have now confirmed this safety [9].

In CLEOPATRA, a left ventricular ejection fraction of 50% or greater was required for study entry. Left ventricular ejection fraction (LVEF) assessments were carried out every 9 weeks, and either basic two-dimensional echocardiography or multi-gated acquisition scans were permitted. The trial was conducted at 204 centers in 25 countries; 402 patients were included in the cohort that received pertuzumab 840 mg as a loading dose followed by 420 mg every 3 weeks plus trastuzumab 8 mg/kg as a loading dose followed by 6 mg/kg every 3 weeks, plus docetaxel 75 mg/m^2 every 3 weeks. LVEF declines of 10% or more to a value of less than 50% were reported in 3.8% of patients in that group. In the report by Yu et al. [9], the regimen is similar but for the use of paclitaxel 80 mg/m^2 rather than docetaxel. Yu et al. reported 2 patients (3%) who experienced asymptomatic declines in LVEF.

Contractile dysfunction is primarily assessed by declines in the LVEF, and that was the parameter used to assess cardiotoxicity in CLEOPATRA. LVEF assessments are not perfect. The basic ultrasound examination demonstrates interobserver variation; in addition, a host of physiological changes affect the final LVEF value. Drug-related declines are evident only after substantial impairment of function and inability to fully compensate for the loss of contractile elements. As was emphasized by Yu et al., newer techniques have demonstrated greater precision, accuracy, and sensitivity [9]. We may now be able to identify those patients who are at especially high risk and offer mitigating strategies earlier in an effort to spare myocytes. Fortunately, this strategy, as emphasized by Yu et al., is gaining momentum. On the other hand, earlier recognition of subclinical toxicity has a potential danger, also clearly recognized by Yu et al., that might result in treatment decisions compromising optimal oncologic efficacy.

Safety of the combination of pertuzumab and trastuzumab was established in CLEOPATRA, yet CLEOPATRA used conventional LVEF determinations to define events and did not include troponin determinations or strain imaging. In their report, Yu et al. confirm cardiac safety even when these more-sensitive cardiac testing procedures are used [9]. As the authors point out, a trial incorporating cardiac risk and central review showing enhanced recognition of functional impairment would be hugely important to help establish the optimal level of surveillance and add perspective to these new modalities. Because the level of toxicity was not sufficiently high to detect meaningful differences in the Yu et al. study, this may not have been the optimal patient population in which to detect the incremental benefit of more sensitive approaches.

It is time to recognize that a modification in the recommended monitoring schedule of some regimens may be justified. Even as guidelines are evolving, an evidence-based monitoring schedule rather than one based on the schedules of prior clinical trials that ultimately showed considerable cardiac safety is clearly needed. Cardiologists and oncologists must incorporate new safety data into guidelines lest potentially wasteful, expensive, and probably unnecessary monitoring for regimens with demonstrated cardiac safety are perpetuated. We applaud the work of Yu et al. for using cardiac testing with enhanced sensitivity as well as for having confirmed the cardiac safety of the dual anti-HER2 regimen, thereby moving us forward as we strive to achieve the mutual goals that define cardio-oncology.

Disclosures

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References

1. Ewer MS, Von Hoff DD, Benjamin RS. A historical perspective of anthracycline cardiotoxicity. Heart Fail Clin 2011;7:363–372.

2. Ewer MS, Ali MK, Mackay B et al. A comparison of cardiac biopsy grades and ejection fraction estimations in patients receiving Adriamycin. J Clin Oncol 1984;2:112–117.

3. Suter TM, Ewer MS. Cancer drugs and the heart: Importance and management. Eur Heart J 2013;34:1102–1111.

4. Swain SM, Whaley FS, Gerber MC et al. Cardioprotection with dexrazoxane for doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol 1997;15:1318–1332.

5. Legha SS, Benjamin RS, Mackay B et al. Reduction of doxorubicin cardiotoxicity by prolonged continuous intravenous infusion. Ann Intern Med 1982;96:133–139.

6. van Dalen EC, Michiels EMC, Caron HN et al. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. Cochrane Database Syst Rev 2010;CD005006.

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7. Cardinale D, Sandri MT, Colombo A et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004;109:2749–2754.

8. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–792.

9. Yu A, Manrique C, Pun S et al. Cardiac safety of paclitaxel plus trastuzumab and pertuzumab in patients with HER2-positive metastatic breast cancer. ***The Oncologist*** 2016;21:418–424.

10. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: Time to recognize a new entity. J Clin Oncol 2005;23:2900–2902.

11. de Korte MA, de Vries EG, Lub-de Hooge MN et al. 111Indium-trastuzumab visualises myocardial human epidermal growth factor receptor 2 expression shortly after anthracycline treatment but not during heart failure: A clue to uncover the mechanisms of trastuzumab-related cardiotoxicity. Eur J Cancer 2007;43:2046–2051.

12. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol 2010;7:564–575.

13. Swain SM, Baselga J, Kim SB et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372:724–734.

14. Swain SM, Ewer MS, Cortés J et al. Cardiac tolerability of pertuzumab plus trastuzumab plus docetaxel in patients with HER2-positive metastatic breast cancer in CLEOPATRA: A randomized, double-blind, placebo-controlled phase III study. ***The Oncologist*** 2013;18:257–264.

EDITOR'S NOTE: See the related article, "Cardiac Safety of Paclitaxel Plus Trastuzumab and Pertuzumab in Patients With HER2-Positive Metastatic Breast Cancer," by Anthony F. Yu, on page 418 of this issue.

For Further Reading:

Sandra M. Swain, Michael S. Ewer, Javier Cortés et al. Cardiac Tolerability of Pertuzumab Plus Trastuzumab Plus Docetaxel in Patients With HER2-Positive Metastatic Breast Cancer in CLEOPATRA: A Randomized, Double-Blind, Placebo-Controlled Phase III Study. ***The Oncologist*** 2013;18:257–264.

Implications for Practice:

CLEOPATRA was the first phase III trial in which the combination of pertuzumab with trastuzumab and docetaxel was studied in patients with HER2-positive metastatic breast cancer in the first line. As therapy with trastuzumab, especially in combination with anthracyclines, has been associated with cardiac dysfunction, it was important to investigate the cardiac tolerability of the study combination of two HER2-targeted antibodies, trastuzumab and pertuzumab, with docetaxel. The analyses showed that the combination of pertuzumab, trastuzumab, and docetaxel was not associated with an increase in cardiac dysfunction, especially LVSD, compared with placebo, trastuzumab and docetaxel. Cardiac adverse events were largely reversible and clinically manageable. Despite the encouraging findings, the authors recommend the regular cardiac monitoring of patients while long-term safety data with pertuzumab-trastuzumab-based treatment are still being accrued in clinical practice.

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