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EDITORIALS

Entering My Final Year As Editor-in-Chief of *Journal of Clinical Oncology*

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After the 2010 American Society of Clinical Oncology (ASCO) Annual Meeting, I knew why Mark Twain felt compelled to write "The reports of my death are greatly exaggerated." It was wonderful for so many people to congratulate me on a job well done and for them to inquire about what I would do with my time. The time to answer that question has not yet come.

Perhaps a few words of explanation are required. I was appointed by Joseph S. Bailes, who was then president of ASCO, in early 2000 after a search by the publications committee, and I assumed the role of Editor-in-Chief of *Journal of Clinical Oncology* (*JCO*) at the 2001 ASCO Annual Meeting. The ASCO bylaws limit the term of the editors of ASCO journals to a maximum of two 5-year terms, and my tenure will end a year from now. The past 9 years have been a great honor and pleasure for me, and I am glad to have a 10th year to lead *JCO*. To ensure continuity of *JCO*, a similar search was completed in the fall of last year, and Stephen A. Cannistra, a former associate editor and a current consultant editor for *JCO*'s Biology of Neoplasia section, was selected as the fourth Editor-in-Chief of *JCO*, with his term starting at the 2011 ASCO Annual Meeting. During the next year, we will be working together to continue to improve *JCO* as the irreplaceable resource for oncology that it has become. *JCO* is a much more complex enterprise than it was a decade ago, and much work will be required to make next year's transition as seamless as possible. Everyone involved is dedicated to making my 10th year as Editor-in-Chief as productive as possible in recognition of the fact that the readers of *JCO* deserve nothing less.

Meanwhile, as I reported to the ASCO Board of Directors at its recent meeting, *JCO* has never been stronger. Submissions steadily increase, and the quality of the manuscripts is better than ever. Given the limitations in space, the increase in submissions has inevitably led to a more stringent acceptance rate as we strive to keep the quality of *JCO* high and keep it competitive with the best medical journals. In recognition of our success, we learned just after the 2010 ASCO Annual Meeting that *JCO*'s impact factor increased again to 17.793—more than a 4-point increase during the last 4 years.

JCO remains innovative among its peers with translated editions in many languages, the broadest possible range of published topics, and the ability to seek improvements in coverage of the entire landscape of oncology. As an example of this, we have increased the number of articles published on the subject of hematologic malignancies by more than 30% in the last 2 years, attracting a new audience of international authors and readers.

The future looks just as bright or even brighter as the editors and I look ahead to and plan for the coming year. Changes will include making randomized phase II and III protocols available to readers, podcasting, continuing medical education credits for our dedicated reviewers, and many other enhancements. The only aspect of *JCO* that should not change is the continued publication of that which is new, true, and practice changing in clinical oncology.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Troponin I Provides Insight Into Cardiotoxicity and the Anthracycline-Trastuzumab Interaction

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Great strides have been made in the treatment of breast cancer during the last few decades, yet cardiotoxicity of anticancer agents remains a substantial concern. Although both anthracyclines and trastuzumab are associated with left ventricular dysfunction and heart failure, there is now general agreement that major differences exist regarding the nature of their cardiotoxicity. Anthracycline

cardiomyopathy has been well characterized, but features of trastuzumab cardiotoxicity, such as the precise mechanism, capacity for recovery, long-term implications, and overall clinical importance, remain controversial. Some of the uncertainty regarding trastuzumab stems from the fact that human epidermal growth factor receptor 2 (HER2) – positive patients with breast cancer are commonly treated with both trastuzumab and an anthracycline, and isolating effects of either agent from a potential synergistic interaction between them presents a dilemma.

The article in this issue of *Journal of Clinical Oncology* by Cardinale et al[1] identifies a subgroup of patients treated with trastuzumab who exhibit elevations in serum troponin I. These patients were more likely to develop trastuzumab-induced cardiotoxicity (TIC) and less likely to recover, even when treated for cardiac dysfunction. Furthermore, elevated troponin predicted a 25-fold increase in risk for major adverse cardiac events. Perhaps more significant than these important findings, this study offers the opportunity for us to rethink some of what we know—or think we know—about cardiotoxicity of trastuzumab, anthracyclines, and the sequential use of these agents.

Several important clues emerge from the study. First, prior anthracycline use was found to be a significant risk factor for the development of TIC. Second, the cumulative anthracycline dose was significantly higher in those who developed TIC. Third, elevation of troponin I (with all of its prognostic implications) was observed exclusively in patients with prior anthracycline exposure. Fourth, troponin I elevation was found in seven patients prior to trastuzumab therapy, despite normal left ventricular ejection fraction, suggesting ongoing anthracycline-mediated myocyte damage that would have otherwise gone unrecognized. These findings can now be integrated into our existing fund of knowledge regarding cardiotoxicity in patients with sequential exposure to anthracyclines and trastuzumab and can help us understand the apparent synergy that exists between anthracyclines and trastuzumab with respect to cardiotoxicity.

We know that anthracyclines destroy myocytes. This is well established from the cumulative dose versus congestive heart failure relationship, from extensive myocardial biopsy experience, from the mathematical predictability of cardiac failure with dose, and from the important observation that troponin I levels are elevated after anthracycline administration, predicting later heart failure.[2-5] It is less well understood what happens to myocytes after trastuzumab exposure and what happens when anthracyclines and trastuzumab are given concomitantly or sequentially. We have known for some time that the cardiotoxicity of trastuzumab is different from that of the anthracyclines in that it is not cumulatively dose-related. In the metastatic setting, trastuzumab has been used for extended periods without predictable heart failure; furthermore, a trastuzumab arm testing 2-year exposure is part of the ongoing HERA (Herceptin Adjuvant) trial.[6,7] The cardiac biopsy specimens that have been evaluated after trastuzumab exposure have not shown any anthracycline-like changes or changes that suggest significant myocyte destruction.[6] On the clinical level, several trials have shown, and Cardinale et al[1] confirm, the reversibility of cardiac dysfunction.[7,8] As a window through which to observe pure trastuzumab effects, the FinHer (Finland Herceptin) trial and the nonanthracycline arm of the Breast Cancer International Research Group 006 (BCIRG 006) trial reported a low level of cardiotoxicity.[9,10] These facts, along with the virtual absence of deaths in the trastuzumab arms of the adjuvant trials, beg the question: how inherently cardiotoxic is trastuzumab by itself?

One compelling, albeit unconfirmed, observation is the finding that the greater the time interval between the administration of the anthracycline and trastuzumab, the less cardiotoxicity we see.[11] When anthracyclines and trastuzumab were administered concurrently, the incidence of New York Heart Association class III or IV heart failure was 16%.[12] The interval between anthracycline and trastuzumab was approximately 3 weeks in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and BCIRG 006 trials, which demonstrated incidence of class III or IV heart failure at 4.1% and 1.9%, respectively.[8] The delay in time was nearly 3 months in the HERA trial, which reported an incidence of heart failure of 0.6%, approaching that of the nonanthracycline arm of the BCIRG 006 trial (0.4%).[7,9] Although Cardinale et al[1] do not provide detailed information regarding the timing of anthracycline and trastuzumab administration, a similar phenomenon is suggested in their data; positive troponin was found before trastuzumab or after the first two cycles in 30 patients, whereas only two patients presented with positive troponin between cycles 3 and 7. These observations provide support for the concept of a vulnerable time period early after anthracycline administration when the heart is more susceptible to additional insult from trastuzumab.

Other studies have provided mechanistic insight into the anthracycline-trastuzumab interaction. HER2 is expressed in the heart, and preclinical studies suggest that downstream-signaling pathways are important for cardiac myocyte survival and adaptation to stress.[13] Inhibition of these pathways after an insult such as anthracycline exposure could thus attenuate the heart's repair mechanisms. Indeed, de Kort et al[14] demonstrated that myocardial HER2 is upregulated in humans shortly after anthracycline administration, providing a plausible mechanism for the vulnerable-window hypothesis.

A paradigm begins to emerge, supported by some crucial pieces of evidence provided by Cardinale et al[1] and illustrated in Figure 1. Anthracycline administration causes initial oxidative damage to cardiac myocytes. A threshold effect exists whereby those cells sustaining sufficient damage undergo apoptosis or necrosis and release troponin, whereas the remaining injured myocytes undergo repair processes. These cells remain temporarily vulnerable, and some eventually go on to die, thereby underscoring the observation by Cardinale et al that patients may present elevated troponin before trastuzumab administration. Then enters onto this stage trastuzumab, which by itself has the potential to cause the well-documented, reversible impairment of the contractile elements but which also now binds to the vulnerable anthracycline-altered myocytes with upregulated HER2 and inhibits cell repair. Myocytes that might have otherwise undergone repair experience cell death, and troponin I continues to be detectable. This model could explain why some patients fail to fully recover left ventricular function after TIC, when the more isolated trastuzumab injury is so often reversible. The anthracycline-trastuzumab interaction yields significant cardiotoxicity beyond the levels experienced in the BCIRG 006 nonanthracycline arm.

What we seem to be seeing is a modulating effect of trastuzumab on the vulnerable and previously damaged myocyte. Trastuzumab has a low inherent capacity to cause myocyte death but a far greater potential to modify the natural history of cell damage and repair that follows anthracycline exposure; with regard to cardiotoxicity, it constitutes a highly potent modulator of anthracycline toxicity. Such a concept explains the high levels of cardiotoxicity observed in the

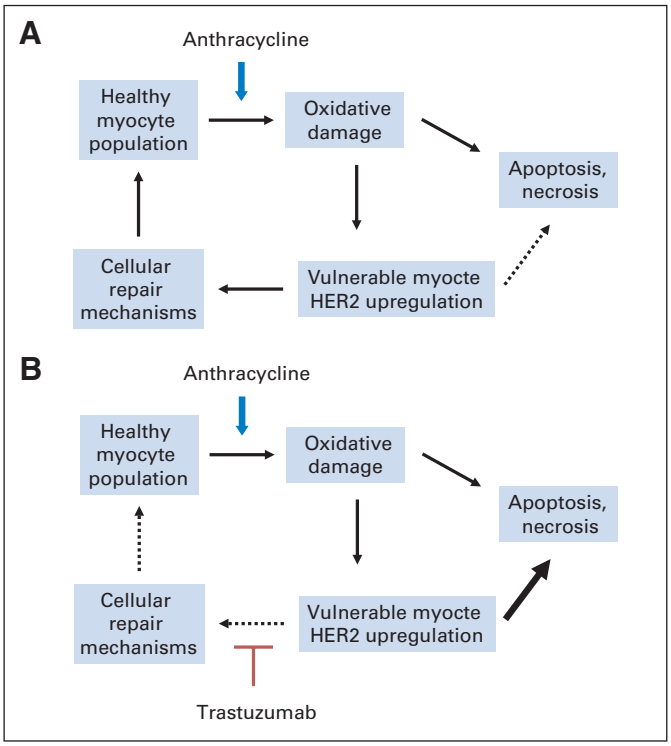

Fig 1. (A) Simplified flow diagram of myocyte injury after anthracycline administration. Cell death is preceded by a period of vulnerability during which cell repair may take place. (B) The addition of trastuzumab inhibits cell repair, compounding the loss of cardiac myocytes. HER2, human epidermal growth factor receptor 2.

pivotal trials: the long-term tolerability of trastuzumab with limited cardiac sequelae in both the adjuvant and the metastatic settings, the observation—now also confirmed by Cardinale et al—that reintroduction of trastuzumab after a decrease in cardiac contractibility followed by sufficient time for recovery is usually tolerated, and new data regarding troponin release. With trastuzumab as a modulator of cell repair, we can appreciate why some patients have troponin elevations before trastuzumab administration, why elevated troponin after trastuzumab is a marker for worse prognosis, and why many—but not all—patients do well after experiencing some degree of dysfunction after trastuzumab.

The puzzle is not entirely solved, and uncertainties still exist. Buzdar et al[15] reported that concurrent epirubicin and trastuzumab can be well tolerated, albeit with relatively low cumulative dosages of epirubicin (an anthracycline that may be less cardiotoxic than doxorubicin). Troponins were assayed in some of these otherwise healthy patients and were not elevated. Gianni et al[16] have also reported low cardiotoxicity with pegylated liposomal doxorubicin and trastuzumab. Were the added effects simply not sufficiently high to reach the thresholds of toxicity? It may be that, with more modern regimens, concomitant anthracycline and trastuzumab can be safely administered as long as due caution, consideration of cardioprotection, and appropriate monitoring are applied.

As data accumulate, the study by Cardinale et al included, we begin to tease apart the cardiotoxic effects of anthracyclines and trastuzumab, and a proposed mechanism of interaction becomes more plausible. Of course, these interactions must be scrutinized and validated. Long-term follow-up of patients receiving trastuzumab will be essential. But as we move forward, we may well discover that trastuzumab aids and abets in the crime of cell death and amplifies the burden of the anthracycline; in this sense, trastuzumab is far from innocent. But when taken by itself and out of the context of the vulnerable and previously damaged anthracycline-exposed myocyte, we may ultimately discover that trastuzumab is not nearly as guilty for the death of the myocyte as has heretofore been suggested.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Multigene Assays to Improve Assessment of Recurrence Risk and Benefit From Chemotherapy in Early-Stage Colon Cancer: Has the Time Finally Arrived, or Are We Still Stage Locked?

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Worldwide, colorectal cancer is the third most common cancer after lung and prostate cancer in men and breast cancer in women.[1] As with the majority of cancers, long-term survival is dependent on the stage of the disease at diagnosis. For example, patients with stage I colon cancer have a 5-year survival rate higher than 90%; this rate decreases to between 72% and 83% in patients with stage II and between 44% and 83% in those with American Joint Committee on Cancer stage III.[2] However, the current staging system fails to provide an accurate assessment of the risk for individual patients. For example, the finding that patients with stage IIB disease have a worse prognosis than patients with stage IIIA disease indicates the need to develop better tools.[2]

The limitations of the current staging system may interfere with our capacity to deliver optimal clinical care, given that the decision to administer adjuvant chemotherapy after surgery is mostly based on this classification system. In patients with stage III colon cancer, adjuvant therapy is widely considered the standard of care, and its administration has been endorsed, among others, by the American Society of Clinical Oncology (ASCO)[3,4] and the European Society for Medical Oncology.[5] During the last decade, the schedule and duration of adjuvant treatment in colon cancer has changed from a 12-month course of bolus fluorouracil (FU) and levamisole combination[6] to a 6-month course of either infusional FU combined with leucovorin (LV) and oxaliplatin[7,8] or an oral fluoropyrimidine such as capecitabine.[9] On the other hand, the role of adjuvant chemotherapy is more controversial in patients with stage II disease.[10-12] In this regard, efforts have been directed at identifying clinicopathologic features or molecular characteristics that result in a worse prognosis in patients with stage II disease to identify patients within this group to receive adjuvant therapy.[4,5,13] A number of worse prognosis risk factors have been identified in stage II disease, including an inadequately low number of sampled nodes at surgery ($\leq$ 12); T4 tumors; obstruction or bowel perforation at initial diagnosis; poorly differentiated histology; vascular, lymphatic, and perineural invasion; a high preoperative carcinoembryonic antigen level; and the presence of indeterminate or positive resection margins.[4,5,13] Molecular biomarkers have also been used to identify subsets of patients with a higher or lower risk of recurrence and the benefit that they may derive from adjuvant treatment. For example, mismatch repair deficiency or high microsatellite instability (MSI-H) may identify a small population of patients with stage II who may derive no benefit or may even experience deleterious effects from adjuvant FU/LV-based chemotherapy.[4,5,13,14]

Single gene–based markers have been widely investigated to determine their roles as prognostic or predictive biomarkers in the setting of adjuvant therapy for colon cancer. Although multiple single gene–based marker candidates have been proposed, the results have been either contradictory or not robust enough, with the notable exception of MSI. Popat et al[15] published a systematic review of 32 studies addressing the potential prognostic value of MSI in colon cancer. Briefly, patients with MSI tumors have a significantly better outcome. However, before MSI status is routinely used to influence patient management, validation in the context of prospective clinical trials is required. The E5202 study (NCT00217737) has been designed to validate the prognosis of MSI. Patients are being stratified according to disease stage (IIA *v* IIB) and MSI (MSI-H *v* microsatellite stable [MSS] and MSI low). Patients are defined as high risk when they present with MSS or MSI low or loss of heterozygosity (LOH) at chromosome 18q and are subsequently randomly selected to receive adjuvant therapy with FU, LV, and oxaliplatin with or without bevacizumab. Patients with low-risk features such as MSI-H and absence of 18q LOH are assigned to observation only.[16] The somatic LOH at chromosome 18q, a site containing genes related to colorectal cancer,

