Taking survival to heart.

Cardiology & Oncology Partnership
IV Annual International Symposium

October 7–9, 2010
Nashville, Tennessee
Highlighted Proceedings of the
IV Annual International Symposium
of the Cardiology & Oncology Partnership

International CardiOncology Society
Dear Colleagues:

It is my great pleasure to introduce you to the Cardiology and Oncology Partnership which held its Fourth Annual Meeting in Nashville, Tennessee, October 7–9, 2010. The proceedings from this important International meeting are distilled here in a carefully prepared document that represents the most updated developments in the field of cardiac disease in cancer patients. This is a burgeoning area of medical care largely because of the success of cancer therapy and the overlap between the therapeutic targets as well as the demographics of patients who are seen by providers in the disciplines of cardiology and oncology.

This meeting had a combined representation of cardiologists and oncologists who care for patients in governmental, institutional and community-based practices and have extensive experience in the practical decisions that can be difficult about caring for patients with both cardiac disease and cancer. Furthermore, many of these practitioners have been involved in the research that forms the basis of our understanding of treating these clinical situations.

I am honored to present a summary from a portion of this meeting and would encourage all that are interested to learn more about these issues and join our developing consortium, the International CardiOncology Society (http://www.cardioncology.it/).

Please enjoy and join our group of friends!

Sincerely,

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Introduction to IV Annual International Symposium of the Cardiology & Oncology Partnership

Nancy J. Brown, MD
Chair-Elect, Department of Medicine, Vanderbilt

“We need to understand the interplay between cancer and cardiovascular disease if only because these two diseases are prevalent among our aging population and, therefore, will be increasingly coexistent in our patients.”

—Nancy J. Brown, MD

The study by Driver and colleagues showed the incidence of coinciding cardiovascular disease and cancer in the Physician Health Study. We need to understand the interplay between cancer and cardiovascular disease if only because these two diseases are prevalent among our aging population, and, therefore, will be increasingly coexistent in our patients (Figure 1).

![Figure 1. Incidence of Cardiovascular Disease and Cancer in the Physicians Health Study](image)

Adapted from Driver JA et al. BMJ. 2008;337:a2467.

We know that there are ways to protect patients against cardiac damage. Carvedilol, for example, protects against anthracyclines, a class of chemotherapy drugs, that have caused cardiac injury. There are additional studies showing that angiotensin-converting enzyme (ACE) inhibitors may be cardioprotective as well. Understanding which drugs are or will be protective, who should be treated, and how to treat them are issues that will require an understanding of mechanisms. It will require true translational medicine in which we are translating information back from clinical observations to animal models to understand these mechanisms. The question being if ACE inhibitors protect against cardiac injury, could they also have a pro-oncogenic effect?
ACE inhibitors and angiotensin receptor blockers (ARBs) are often confounded in the minds of clinicians, yet they are very different. A meta-analysis published in *Lancet*, suggested that there is a link between ARBs and the onset of cancer.\(^4\) Whether or not this is true remains to be replicated. There are theoretical mechanisms by which ARBs could affect cancer risk or progression of existing cancers. I believe we will be unveiling new physiology as new drugs are developed. This is a real opportunity for personalized medicine.

Vanderbilt Ingram Cancer Center is currently offering screening to cancer patients based on the genetic profile of their tumors. This will allow us to personalize cancer therapies. Because of our advances in this arena, I could imagine that we will eventually be able to predict not only who will have resistant tumors, but who will be at highest risk for cardiovascular complications related to their therapies.

References

Common Mechanisms for Cell Survival and Repair Between Heart and Cancer Cells
Douglas B. Sawyer, MD, PhD
Lisa M. Jacobson Professor of Medicine; Chief, Division of Cardiovascular Medicine; Physician-in-Chief, Vanderbilt Heart & Vascular Institute

“*I think the cell biology of cardiology has been lagging behind the cell biology of oncology, yet perhaps this collaboration of cardio-oncology is helping it to catch up.*”

—Douglas B. Sawyer, MD, PhD

It is simple to understand why cancer drugs also affect the cardiovascular system—all the cells began as one cell and have a common origin and biology. With growth, the cells will eventually look and function differently and that allows us to distinguish them from one another, yet the fundamental signaling mechanisms are common to all of them.
Anthracyclines, for example, are known to induce heart failure. One of the mechanisms is that anthracyclines intercalate into a nucleic acid backbone and interrupt many of the nucleic acid processes including replication and repair that will eventually cause myofilament degradation and myocyte cell death. Many of the studies we are conducting with anthracyclines are trying to get at some of the fundamental mechanisms of cellular repair of cardiac myocytes. We know that cardiac myocytes can undergo normal physiologic hypertrophy, concentric hypertrophy, and eccentric hypertrophy, yet what the mechanisms are and how these processes are regulated is an ongoing investigation (Figure 2).
Many of the signaling diagrams that have come out of these studies show that the mechanisms of cardiac cellular response to injury are the fundamental pathways that cancer therapy targets. These pathways are involved in the proliferation, angiogenesis, and differentiation in neoplasms with the targets amenable to therapeutic interventions in cancer therapy. A study involving RAF inhibitors in melanoma confirmed that the same pathway is part of the mechanism for cardiac myocyte transcriptional regulation of sarcomeric proteins (Figure 3).²

Likewise, there are survival pathways in cardiac myocytes that are the targets of ongoing trials in cancer. Apoptotic pathways in myocytes have emerged as being similar to oncologic apoptotic pathways. Therefore, when we target those pathways in treating cancer, we are augmenting those pathways in cardiac myocytes and promoting cardiac failure.

When asked to predict the future, my colleagues and I sat down and asked ourselves, “What are the pathways that are common to the heart and cancer cells that might be interesting to think about prospectively as opposed to waiting until we have a problem with heart failure? Can we do something to help the oncology community?” What we found were a number of drugs that target all of these pathways and these pathways are present in cancer and heart cells where they regulate important processes. An interesting characteristic about this area of study is that it not only helps oncology, it sometimes can be flipped around and helps us develop our knowledge of heart failure. For example, what we have learned about trastuzumab (Herceptin®) targeting the ErbB2 tyrosine kinase receptor has helped us in trying to develop a ligand for those receptors in the heart as a therapy for heart failure independent of cancer. ERB2 and ERB4, which regulate a number of pathways that are being explored as targets in cancer therapy, are plentiful in the heart, so it is understandable why some targeted chemotherapy may alter cardiac structure and function.

The signaling pathway is regulated in the heart by stress, so under basal conditions in the adult heart this is fairly quiet. Once there is anthracycline exposure or any oxidant stress (e.g., ischemia or perfusion) this pathway is activated. Fundamentally, the biology of the heart in the cardiovascular system overlaps with any tumor cell. The difference is that the signaling systems go up and down in normal tissue like the myocardium and stay constitutively active in the tumor cells. When a target of therapy is present in the myocardium, a critical question that should be addressed is the timing of signaling activity in other organs. Theoretically, if signal inhibitors are administered during periods of relatively inactive times for those systems in the heart (therapeutic window), the consequences may be reduced compared to times where these systems are actively involved in maintaining cardiovascular structure or function. For example, in the case of trastuzumab (Herceptin®), we know that this drug is not that bad unless it is given in the presence of anthracyclines or cardiac stress. It needs a wider therapeutic window and, unfortunately, we did not know this upfront. As we move forward with new therapies, perhaps understanding when it is okay to use the new drugs (e.g., quiet, inactive system at baseline or active system when stressed) might be a strategy to offset the fact that many of their targets overlap.
Another group of inhibitors that includes Hsp90 has been studied. Hsp90 is a chaperone that stabilizes client proteins (i.e., ErbB2), many of which are in the signaling pathway. Hsp90 is an adenosine triphosphate (ATP)-binding protein that means it requires ATP to do its job. A number of compounds have been developed that bind to Hsp90 and inhibit its activity. If this happens, then the thought is that there is degradation of all the signaling proteins that are important for cancer growth, so there is a multitarget response. Whether or not this is a good idea in the heart is open for debate. It is interesting, however, that if you eliminate the Hsp90 activity in the heart—the signaling proteins are degraded—there is an activation of a heat shock response that involves a cardioprotective heat shock protein 70 (Hsp70). So, with all of these therapies coming down the road, we are still trying to figure out who is going to benefit, who is going to have a problem, and what is the correct situation in which to administer? The cardio-oncology community has to lead the way.

References

Thrombosis in Cancer Patients: What are the Treatments and the Challenges?
Agnes Lee, MD, MSc, FRCPC
Director, Thrombosis Program Vancouver Coastal Health, British Columbia

“Many know that cancer-associated thrombosis is a common cause of mortality and morbidity in these patients. What you may not know is that it is the leading cause of death in cancer patients secondary to the progression of their underlying neoplastic disease.”

—Agnes Lee, MD, MSc, FRCPC

The median survival of cancer patients with thrombosis is only about six months, so it is one of the poorest prognostic factors in oncology patients. When these patients develop thrombosis, they are removed from their first-line therapy because the thrombosis interferes with their cancer treatment and is considered an adverse event. As a result, the patients may not receive the most optimal treatment for their underlying cancer; therefore, thrombosis precipitates and prolongs hospitalization, which in turn, can increase patients’ morbidity and significantly increases
healthcare resource utilization. It has been estimated that a single case of pulmonary embolism (PE) costs over $10,000 to treat and this adds a tremendous amount of emotional and economic burden to the patients and their families.

The incidence of cancer-associated thrombosis is on the rise due to improved oncology outcomes that are keeping patients alive longer; more advanced disease, which is one of the strongest predictors of thrombotic complications; the administration of more thrombogenic regimens; and the aging population. In order to improve patient outcomes, we need to provide primary prophylaxis when indicated because this is where we are going to have the biggest impact in reducing the disease burden; diagnose thrombotic disease more accurately and efficiently—symptoms of thrombosis should not be attributed to other underlying diseases or complications; and provide optimal treatment when the diagnosis is made.

Primary prophylaxis for thrombosis has best been studied in the surgical population and has become the standard of care for all patients undergoing surgery, especially cancer patients. The two best agents that have been investigated for primary prophylaxis are low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH). LMWH and UFH are quite comparable in terms of the important clinical outcomes (e.g., PE, death, major hemorrhage, or hematomas), efficacy, and safety. The difference lies in that once-daily administration of LMWH is more convenient than two or three times daily administration with unfractionated heparin. In addition, it has been demonstrated that LMWH is, in fact, more cost-effective than unfractionated heparin, certainly for medical prophylaxis because of reductions in complications (e.g., heparin-induced thrombosis), dose errors, needle-stick injuries, and so forth. For these reasons, surgeons are going to use more LMWHs for prophylaxis.

Two large trials researched inpatient prophylaxis for surgical patients: ENOXACAN and Canadian Colorectal Study.\(^1,2\) There was little difference between UFH and a LMWH (enoxaparin) given once daily or UFH three times a day versus enoxaparin; however, despite the standard, routine prophylaxis, the incidence of thrombosis in these patients is still about 15-20% based on venographic thrombosis outcomes that strongly correlate to clinically important thrombosis. This is an area for improvement.

One way to reduce the incidence of thrombosis is to provide extended thrombo-prophylaxis. This has been investigated in the ENOXACAN II and FAME studies where cancer patients undergoing abdominal or pelvic surgery were randomized to continue LMWH or receive placebo. There was a statistically significant reduction in thrombosis when patients were given LMWH beyond their hospitalization up to 30 days.\(^3\) Extended prophylaxis has become the standard of care for cancer patients undergoing surgery in Europe, yet this is not the case in North America. This is because some investigators believe that venographic trials may not represent clinical disease and the cost of LMWH is prohibitive for most patients to continue beyond hospitalization. There is new data to suggest that venographic outcomes in these studies do translate to important clinical outcomes.\(^4\)
The @RISTO study investigated a prospective cohort of 2300 surgical patients undergoing curative surgery for abdominal or pelvic cancer. These patients were followed for clinical deep vein thrombosis (DVT) or PE as a primary outcome. The incidence of thrombosis decreased while the patients were receiving prophylaxis in the hospital. Upon discharge, however, the incidence of thrombosis increased, peaking at approximately the third week post-surgery. Researchers also found that despite standard prophylaxis, the symptomatic thrombotic event rate was still approximately 2% up to a month post-surgery and the overall mortality was 1.7% with half of these deaths due to PE, a potentially preventable problem. This study also identified several independent risk factors for thrombosis in high-risk patients, such as those with a previous history of thrombosis (which increases the risk of having a thrombotic event six-fold compared to other surgical patients), undergoing anesthesia for more than two hours, post-operative bed rest for more than four days, having an advanced tumor, and being in an older age group. If extended prophylaxis is not provided across the board to all surgical patients, then at least high-risk surgical patients may be considered.

Another study called the Million Women Study is really convincing physicians to change their practice. This was a large study that followed 1 million middle-aged women in the United Kingdom between 1996 and 2001. These patients were prospectively assessed for the development of symptomatic PE, DVT, or death from VTE using national hospital admission databases. These women were followed from their baseline mammogram, unrelated to surgery or thrombosis, and benign cancer screening program prospectively on whether or not they underwent surgery and what the thrombosis event rate was after that. This study revealed that in the first 12 weeks post-surgery, the risk of thrombosis is about 1 in 140 for any surgery, 1 in 85 if patients undergo cancer surgery (these patients would have received standard thromboprophylaxis), 1 in 45 hip or knee surgery, and about 1 in 115 for vascular surgery. The highest risk group are those patients undergoing hip or knee surgery that are now routinely provided thromboprophylaxis as the standard of care up to 30 days. This study also confirmed that the peak incidence of symptomatic thrombosis is approximately three weeks after hospitalization or surgery. In addition, the incidence of PE was higher than the incidence of DVT. The risk for outpatient surgery is also lower compared to those who require inpatient hospitalization post-surgery. If these patients had cancer, then the relative risk was 92-fold higher compared to those who did not which is as high as patients undergoing surgery for hip fracture where extended prophylaxis up to 30 days is standard, routine practice.

Therefore, based on these studies, thromboprophylaxis is recommended by the American Society of Clinical Oncology (ASCO) guidelines to be continued for a minimum of 7-10 days post-surgery. Systems or compliance programs need to address how to get patients to continue this minimum duration of routine thromboprophylaxis once they leave the hospital. The ASCO guidelines also now recommend that patients with additional high-risk factors (e.g., previous history of thrombosis, extended surgery or mobilization, advanced tumor, advanced age) have up to four weeks of thromboprophylaxis.
The next large group of patients who need primary prophylaxis are cancer patients receiving outpatient chemotherapy. The first study of this group was conducted in 1994 and looked at warfarin therapy in women undergoing outpatient chemotherapy for Stage IV breast cancer. Warfarin was effective in reducing the incidence of symptomatic thrombosis by 85%. Despite this positive study, warfarin was not accepted as standard prophylaxis in this population because the incidence was not high enough and it is difficult to use in cancer patients.

Other trials looked at the use of LMWH for primary prophylaxis because it is more convenient to use—it doesn’t need monitoring and there is no interaction with chemotherapy—yet none of them showed a statistically significant reduction in venous thrombosis. Therefore, because of these trials, the 2007 ASCO guidelines did not recommend routine prophylaxis for outpatients receiving chemotherapy except for those who have multiple myeloma receiving dexamethasone due to the incidence of thrombosis being up to 25% depending on the chemotherapeutic regimen. To date there has been no single, randomized control trial looking at thromboprophylaxis in this population.

There have been other studies that will change the next revision of the ASCO guidelines. The PROTECHT study was a multicenter, double-blind, placebo-controlled, randomized controlled study where patients with advanced lung, breast, gastrointestinal, pancreas, ovarian, head and neck cancer received nadroparin, a LMWH commonly used in Europe, or placebo for the duration of their four-month chemotherapy. There was a significant reduction in thrombotic events in the patients who received nadroparin with no statistically significant difference in the incidence of bleeding. Despite the reduction in symptomatic thrombosis, there was no difference in death or mortality rates. This makes some question whether or not thromboprophylaxis is necessary.

Recently two large studies, which focused on patients with advanced pancreatic cancer, concluded that the mortality is improved with primary prophylaxis. The first, CONKO 004 Trial, included 312 patients with advanced pancreatic cancers that were randomized to receive standard chemotherapy with gemcitabine or gemcitabine with enoxaparin (given at half a therapeutic dose). The primary outcome was symptomatic thrombosis and fatal PE at 12 weeks. There was a dramatic reduction in this outcome with enoxaparin and no difference in bleeding. The second study, FRAGEM Trial, confirmed the results of the CONKO 004 Study. Similarly designed, the FRAGEM Trial looked at 123 patients with advanced pancreatic cancer, randomized them to gemcitabine or gemcitabine plus dalteparin. The primary outcome was symptomatic thrombosis and fatal PE at three months. There was a significant reduction in symptomatic VTE, fatal PE, or sudden death. These were the first two studies to show that primary prophylaxis in a population with a significantly-high incidence of thrombosis will improve survival in cancer patients without giving them more toxic chemotherapy.

More recently, a meta-analysis showed that LMWH does reduce the risk of symptomatic thrombosis. If you took the results for the pancreatic population, clearly with the two positive studies, there was a significant reduction. In addition, there does not seem to be any major bleed-
ing when using LMWH in these patients either.

Overall there seems to be a trend to recommend primary prophylaxis in ambulatory patients receiving outpatient chemotherapy. Perhaps the patients with the highest risks, where the benefit-to-risk ratio would be maximized and the risks associated with anticoagulation would be minimized, are whom we should target.

The first clinical assessment model to determine whether or not a patient has a high-risk of thrombosis and should go on to receive thromboprophylaxis has been developed—Khorana Risk Assessment Model.\textsuperscript{14} This model was developed using a multivariate analysis and defined five risk factors that predict thrombotic events. Patients are grouped on site of cancer and scored accordingly. If patients had a low-risk score with none of those risk factors, the risk of developing thrombosis was only about 0.8%. If patients have an intermediate score of 1 to 2, the risk is about 2%; if the score is 3 or higher, the risk is 7%. The scoring mechanism was validated using internal data and a group in Vienna validated the model externally using their prospective database (e.g., Cancer and Thrombosis Study, the CATS study). When the validation is published, it will be the first and the simplest risk-scoring model to identify patients for individualized therapy.

In summary, cancer-associated thrombosis is a common problem with poor outcomes in outpatients. Prophylaxis is effective, yet should be used in selected patients. The risk assessment models are helpful in identifying the high-risk populations and clinical trials will demonstrate their usefulness in helping manage patients and further reduce the burden of disease in this population.

### References


Cardiac Biomarkers and Preclinical Detection of Cardiotoxicity

Daniela Cardinale, MD, PhD
Senior Deputy Director, Cardiology Unit, European Institute of Oncology

“Troponin and B-type natriuretic peptide (BNP) give similar information. We observed that both identify patients that will develop cardiac dysfunction, are able to stratify cardiac risk in patients, and predict the degree of late impairment. They [the assays] are similar in the information they provide us, yet are very different. We use troponin-I routinely, in our daily practice, and BNP is [reserved] for cardiopathic patients or those patients with a previous history of cardiac disease.”

—Daniela Cardinale, MD, PhD

The diagnosis of cardiotoxicity can be defined by different approaches. The first is based on the presence of heart failure symptoms and it dates back to 1967 in children treated with anthracyclines—this was the first observation of cardiotoxicity.1 By using this approach, we make an extremely late diagnosis. Another possible approach is based on the asymptomatic reduction in left ventricular ejection fraction (LVEF). By using this approach, we also make a late diagnosis and by that time considerable myocardial cell loss has already occurred and the cardiac damage is, in most cases, progressive and not reversible.

The clinical response to modern heart failure therapy in a patient with asymptomatic and symptomatic anthracycline-induced cardiomyopathy was evaluated.2 The results of our study clearly showed that the percentage of patients undergoing a complete recovery of cardiac func-
tion progressively decreased as the time elapsed from the conclusion of anthracycline-containing therapy while the beginning of heart failure therapy increased. After six months, complete recovery from cardiac dysfunction was not observed in any patient. This emphasizes the crucial importance of an early diagnosis of cardiotoxicity in order to prevent irreversible cardiac dysfunction.

Today we can detect cardiotoxicity at a very early phase, long before any changes in LVEF. We have the possibility to focus in on the cardiac injury by using biomarkers, such as troponin-I. A review highlighted that troponin-I could be considered the gold standard translational biomarker for myocardial injury and cardiotoxicity from different etiologies. Troponin-I has several advantages—high cardiac specificity, high sensitivity, a wide diagnostic window. This approach is minimally invasive, less expensive than an echocardiogram, and in particular, safer than a nuclear evaluation of cardiac function without irradiation for the patients, can be easily repeated, and the results do not depend on the expertise or experience of the operator. Ten years ago, we started measuring troponin-I in high-dose chemotherapy-treated patients. There was a troponin-I increase in 32% of patients in the first 72 hours after chemotherapy and we observed a significant decline in LVEF in the following months in these patients only. In addition, we found a strong relationship between the maximal value of troponin-I per patient and the degree of LVEF drop. This biomarker, therefore, is able to give us two kinds of information early on before there is any decline of LVEF. The first is qualitative which allows us to identify patients who will develop cardiac dysfunction. The second is quantitative meaning the maximal value of troponin-I reflects the degree of the future impairment.

More recently, we evaluated troponin-I in a larger population with longer follow-up and measured troponin-I after one month from the conclusion of chemotherapy. The majority (70%) of patients did not have an increase in troponin-I (low-risk), 21% showed only a transient increase (intermediate-risk), and 9% showed a persistent increase of troponin-I (high-risk). Only the troponin-I-positive patients had a significant decline in LVEF in the following months, yet this decline was significantly more marked in patients with persistently high troponin-I. In parallel, 84% of patients with persistently high troponin-I experienced a cardiac event during the 3.5-year follow-up versus 37% of patients with only a transient increase of the marker and only 1% of patients with negative troponin-I. The troponin-I release pattern identifies patients at different risk levels for cardiotoxicity. Given the high negative predictive value of troponin-I, we can accurately identify patients at low-risk, the majority, who do not require close cardiac monitoring and provide the opportunity to plan preventative strategies in selected high-risk patients in order to prevent the development of asymptomatic and symptomatic cardiotoxicity.

In our studies, we observed increased troponin-I in patients treated with chemotherapeutic regimens containing anthracyclines and those treated with non-anthracycline containing regimens. This suggests that an absolutely safe chemotherapy regimen for the heart does not exist. Clinically we observed an increase of troponin-I in patients treated with standard-dose chemotherapy, particularly if that regimen contained doxorubicin, and in patients treated with non-anthracycline-
based regimens that were preceded by doxorubicin. From our experience, a scheme containing epirubicin, not doxorubicin, appears to be less cardiotoxic.

More recently, an increase of troponin-I was found in patients treated with new antitumoral agents (e.g., trastuzumab, lapatinib, bevacizumab, rituximab). In all cases, the predictive value of troponin-I was confirmed in terms of LVEF reduction and occurrence of cardiac events. Therefore, we suggest the use of troponin-I in the assessment of cardiotoxicity of old and new antitumoral agents, regardless of the mechanism underlying the cardiac toxic effect. Perhaps the release of troponin-I is a common final pathway.

Let’s discuss trastuzumab-induced cardiotoxicity briefly. Trastuzumab has lead to a significant breakthrough in the treatment of breast cancer and is currently considered part of the standard regimen for the treatment of this disease. Unfortunately, the use of trastuzumab has resulted in an unexpectedly high incidence of cardiotoxicity, particularly when it is administered in association with anthracycline. Fortunately, it has also been reported that the clinical outcome from this form of cardiotoxicity is more favorable than that induced by anthracyclines and, in most patients, LVEF improved after the withdrawal of the drug and commencing heart failure therapy. Although preliminary favorable long-term data are emerging, some concerns regarding the early diagnosis and management of trastuzumab-cardiotoxicity still exists and trastuzumab is often permanently discontinued in patients who develop cardiac dysfunction which has a possible negative impact on their oncologic outcome.

Risk factors for trastuzumab-induced cardiotoxicity have not been clearly identified. Cardiac risk stratification by biomarkers in patients treated with trastuzumab had never been evaluated until we investigated the role of troponin-I in this setting. Patients (n=251) treated with trastuzumab in our institution were evaluated. The cardiology monitoring included a LVEF evaluation every three months and troponin-I evaluation immediately before and after each cycle of trastuzumab. The primary endpoint was the occurrence of cardiotoxicity defined as an absolute decrease greater than 10% absolute points in resting LVEF associated with a decline below the normal limit value (50%). If cardiotoxicity occurred, trastuzumab was discontinued and a standard heart failure treatment with angiotensin-converting enzyme (ACE) inhibitors and beta-blockers was initiated. Recovery from cardiotoxicity was defined as a LVEF increase greater than or equal to 50%.

Cardiac dysfunction developed in 32 patients (17% of the study population) (Table 1). No significant difference in terms of age and classical cardiovascular risk factors was determined between the two groups. Troponin I increased during trastuzumab therapy in 62% of patients who developed cardiotoxicity and only in 5% of the patients who did not. Notably, in 7 patients who developed cardiotoxicity, an already increased value of troponin-I was observed prior to trastuzumab therapy, possibly due to a cardiotoxic effect of a previously administered anthracyclines-containing regimen. In addition, the troponin-I increase was associated with a higher incidence of cardiac events—50% incidence in troponin-positive patients versus 2% incidence in troponin-negative patients. After the multivariate analysis, troponin-I positivity was selected as the
only independent predictor of cardiotoxicity. Of the patients who developed cardiotoxicity, 60% recovered from their cardiac dysfunction (Table 2).  

Patients who recovered were younger, more frequently tolerated an association with ACE inhibitors and beta-blockers, and didn’t show an increased level of troponin-I at baseline. Conversely, all patients who did not recover showed an increase of the biomarker during trastuzumab therapy. During the study, troponin-I increased in 36 (14%) patients and the first increase of the biomarker was most frequent after the first cycle of trastuzumab; 19% of patients had increased troponin-I at baseline. After the first two cycles of trastuzumab, 82% of troponin-positive patients were identified—this is quite different from our previous observation in breast cancer patients.

### Table 1. Troponin Predicted Cardiac Events During Study Follow-Up

<table>
<thead>
<tr>
<th>Event</th>
<th>Total (N = 251)</th>
<th>TNI Positive (N = 36)</th>
<th>TNI Negative (N = 215)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe LVEF Reduction (≤ 30%), n (%)</td>
<td>7 (3)</td>
<td>6 (17)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Cardiac Death, n</td>
<td>9 (0)</td>
<td>9 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Acute Coronary Syndrome, n (%)</td>
<td>2 (1)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Acute Pulmonary Edema, n (%)</td>
<td>1 (0.5)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Heart Failure, n</td>
<td>7 (3)</td>
<td>7 (19)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arrhythmias Requiring Treatment, n (%)</td>
<td>5 (2)</td>
<td>2 (0)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Cumulative Events, n (%)</td>
<td>22 (9)</td>
<td>18 (50)</td>
<td>4 (2)*</td>
</tr>
</tbody>
</table>

For each patient only the first event was considered. *P < 0.001 for trend.

### Table 2. Clinical Characteristics of Patients Recovering or Not Recovering From Cardiac Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Recovery 25 (60%)</th>
<th>No Recovery 17 (40%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50 ± 8</td>
<td>56 ± 11</td>
<td>0.047</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (19)</td>
<td>4 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Current or Past Smoker</td>
<td>6 (24)</td>
<td>3 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF Before HRZ Therapy</td>
<td>60 ± 4</td>
<td>61 ± 4</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF at TRZ Withdrawal</td>
<td>44 ± 6</td>
<td>37 ± 6</td>
<td>0.001</td>
</tr>
<tr>
<td>ACEI + BB Association</td>
<td>22 (88)</td>
<td>3 (47)</td>
<td>0.01</td>
</tr>
<tr>
<td>TNI + Baseline</td>
<td>0 (0)</td>
<td>7 (41)</td>
<td>0.001</td>
</tr>
<tr>
<td>TNI + During TRZ Treatment</td>
<td>9 (36)</td>
<td>17 (100)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

treated with high-dose anthracyclines. In breast cancer patients the troponin-positive percentage increased in parallel with the number of anthracycline-cycles administered confirming that the risk for cardiotoxicity is dose dependent.

One possible explanation of the troponin-I release during trastuzumab therapy may be the block of HER2 receptors expressed on cardiomyocytes in addition to tumor cells. This block leads to the loss of survival pathways that are important for the survival and cell integrity because it blunts the effect of a stress signaling pathway activated by previous anthracycline exposure. Trastuzumab could act as a sequential stress on the heart, already vulnerable because of previous anthracycline-exposure, and interfere with repair of myocyte damage. Therefore all troponin-positive patients had been previously treated with anthracyclines in our study. Conversely, in no patients in which trastuzumab was not preceded by an anthracycline was an increase in troponin-I observed. This implies that troponin-I positivity possibly reflects anthracycline-injury facilitated by trastuzumab rather than de novo cardiac damage.

Ewer and colleagues classified chemotherapy-related cardiac dysfunction and the evaluation of troponin-I can provide additional information to assist in further classification. Type 1 due to anthracyclines is often preceded by a troponin-I increase and it is irreversible. Type 2 is not preceded by an increase in troponin-I suggesting its reversibility. A third scenario may exist in patients treated with trastuzumab preceded by anthracyclines. “Type 3” is a trastuzumab-induced dysfunction preceded by a troponin-I increase and is irreversible in many cases. This suggests a mixed etiology—cardiac dysfunction induced by anthracyclines, yet elicited by trastuzumab. Ewer stated in an editorial, “Trastuzumab aids and abets in the crime of cell death and amplifies the burden of anthracycline...” From our results, we know that troponin-I can unmask it.

There is also the observation that early treatment with ACE inhibitors, in patients treated with high-dose chemotherapy (containing mostly anthracyclines) and showing a troponin-I increase post-chemotherapy, can prevent Type 1 cardiac dysfunction. Patients treated with enalapril did not show a significant decrease in LVEF. Conversely, 43% of patients not treated with enalapril reached this endpoint. In clinical practice this prevention is also possible in patients treated with trastuzumab preceded by anthracyclines. In our troponin-positive patients, after the first positivity of the marker, a treatment with enalapril prevented the development of LVEF reduction.

In conclusion, the evaluation of troponin-I in cancer patients predicts the development of left ventricular dysfunction at a very early phase, may discriminate between reversible and irreversible cardiac dysfunction, allows planning for preventive cardiologic strategies, and should be used to define cardiotoxicity.

References


**Common Terminology Criteria for Adverse Events and the Cardiovascular System**

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“It is imperative for the oncology community to work with the cardiovascular/cardiology community to find solutions for our patients.”  
—Scot C. Remick, MD, FACP

What are the challenges of assessing and grading cardiovascular toxicity? A proper clinical evaluation is critical (e.g., risk assessment and exam) and establishment of a baseline (e.g., blood pressure, electrocardiography, urine analysis, etc.) We must try to understand what is normal (e.g., QTc interval, left ventricular ejection fraction [LVEF], blood pressure).\(^1\) There is no harmony of the different grading schemes in oncology and there are inconsistencies among the grading schemes common to cardiology practice. For example, cardiac enzyme leakage was not routinely captured in the cardiology grading criteria, QTc interval has historically presented challenges to regulatory bodies and clinicians, and a more standard approach to evaluating blood pressure is needed.\(^1,3\) Oncologists must get more involved in looking at the cardiovascular safety profile of chemotherapeutic agents (especially vascular endothelial growth factor [VEGF] signaling pathway
[VSP] inhibitors) and the risk of hypertension as these are significant, drug-induced phenomena. It is especially important when administering these agents to cancer patients with multiple underlying comorbidities and cardiovascular problems.

A European study suggests that perhaps blood pressure could be used as a biomarker to achieve a desirable plasma level, thus increase clinical benefit and partial remissions. We must treat our patients and factor in what their underlying cardiovascular risk may be—the more risk there is, the more risk in treating patients with the VSP inhibitors—and whether or not we are in a metastatic setting or an adjuvant setting because the consequences, aggressiveness, and risks that we are willing to accept have to be adjusted based on the setting. In addition, it is becoming more complex in terms of using these drugs. We must know and be sensitive to the drugs that cause QTc prolongation and utilize the safeguards in place in order to administer these drugs safely.

The Cardiovascular Toxicity Grading system was designed to do just that and has recently been revised. This system utilizes the Common Terminology Criteria for Adverse Events (CTCAE).

CTCAE Version 3 was not aligned with MedDRA terminology, therefore the rationale and motivation behind CTCAE Version 4 is a harmonization of the common terminology criteria, to further align with MedDRA terminology, and grading. Grading was derived from the two integrated primary elements: progressive symptomatic/functional status deterioration (e.g., asymptomatic, mildly symptomatic, moderate, severe, life-threatening) and temporal medical intervention. Our focus is on the cardiovascular side effect profiles and acute coronary syndrome was not even included in CTCAE Version 3, so this is an entirely new category in Version 4. The other cardiovascular category revisions include: myocardial infarction and heart failure that were revised to be more user friendly; heart failure grading is no longer linked to a decline in LVEF; left ventricular systolic function now has three grades; hypertension was revised to include prehypertension stages; QTc prolongation elicited a lot of debate and dialog, yet the grading is an improvement over version 3; and troponin-I was not previously captured in the grading, so this is an important addition in grading cardiac dysfunction. These revisions came from a multidisciplinary panel that included oncologists and cardiologists attempting to make physiological sense of the grading in terms of cardiovascular toxicity. Out of curiosity in regards to how cardiac events were graded, a survey of cardiology papers published the New England Journal of Medicine was undertaken. There was a great deal of inconsistency with how events were graded, if they were even graded at all; incomplete safety assessments; no consistency in grading cardiovascular systemic toxicities, especially in new cardiovascular drug trials; and primary endpoints may override safety reporting (being one and the same parameter). The challenge for oncologists is to adapt our grading, at least the CTCAE Version 4, to many of the cardiology trials.

In summary, it has been established that the different chemotherapeutic agents have enormous potential to cause hypertension, acute coronary syndrome, and other cardiovascular side effects. We need to develop a process to risk-stratify our patients, particularly those with underlying cardiovascular comorbidities, and to figure out ways to treat them safely with medications that are
providing new therapeutic gains. It is imperative for the oncology community to work with the cardiovascular/cardiology community to find solutions for our patients.

References

Cardiac Issues in Cancer Patients: Are We Responding Appropriately?
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“Guideline-based therapy is not occurring frequently enough in patients with asymptomatic LV dysfunction.”
—Ronald M. Witteles, MD, FACC

The answer to “Are we responding appropriately to cardiac issues in cancer patients?” is “No, we are not.” The solution is less clear than imagined. Other questions raised are “What is appropriate therapy that we are apparently not responding appropriately to?” and “When should we be screening?” Let’s try to answer one question at a time.

When should we be screening cancer patients for cardiac problems? The doxorubicin label states that the probability of developing impaired myocardial function is estimated to be 1-2% at a total cumulative dose of 300 mg/m² with higher rates of impairment at higher cumulative doses. This is not congestive heart failure (CHF), this is impaired myocardial function, yet the treatment for CHF is noted which includes ACE inhibitors, digoxin, diuretics, low-salt diet, and bed rest. In addition, the labeling says this is where determinations of left ventricular (LV) function should be assessed—particularly with higher cumulative anthracycline doses—yet the dose that warrants screening and the frequency is not stated. Professional medical society recommendations
are notably absent here also. If you are an oncologist giving doxorubicin and looking for additional information regarding when to begin cardiac screening, then this is what you will find—250-300 mg/m$^2$ tends to be the minimum dose for screening. The average dose given for breast cancer chemotherapy is, coincidentally, 240 mg/m$^2$. According to these guidelines the patient would not undergo cardiac screening unless trastuzumab therapy was on the agenda. It should be noted that this data is from 1987 and yet it still holds as the current recommendation.

An influential study conducted 30 years ago by Von Hoff and colleagues retrospectively reviewed, for chemotherapy-induced congestive heart failure, over 4,000 records of patients that had received doxorubicin. The definition of doxorubicin-induced congestive heart failure was clinical signs and symptoms of heart failure believed to be secondary to doxorubicin by the clinician—nothing to do with left ventricular ejection fraction (LVEF) or asymptomatic LV dysfunction. It was clinical heart failure as determined by the oncologist. The conclusion was that the overall incidence of doxorubicin-induced heart failure was quite low (2%) with the inflection point at 550 mg/m$^2$. These numbers are still quoted today. As long as you stay below the cumulative dose of anthracycline, the risk of cardiotoxicity is quite low. With the standard doses that are given for breast cancer or lymphoma (e.g., 200-300 mg/m$^2$) we see an exceedingly low rate (2-3%) and not much of a problem. There is more recent evidence showing that these are underestimates of the true risk of anthracycline toxicity.

Swain and colleagues analyzed cardiac events in patients in the placebo arm of three dexrazoxane trials—these patients were not receiving dexrazoxane. Everybody had a normal LVEF to start and routine Multi Gated Acquisition Scan (MUGA) monitoring throughout the study. A cardiac event was defined as symptomatic CHF or drops in LVEF. Most patients displayed a LVEF drop of greater than 10% to a level below the lower limits of normal. All of a sudden the rates of cardiac events are much higher—at 250 mg/m$^2$ it was 9% and at 550 mg/m$^2$ it was 65%. If you believe these results to be outliers, then review the B31 and N9831 adjuvant breast cancer trials where patients started with a normal LVEF, received anthracycline chemotherapy, and then had another LVEF assessment. If the LVEF had decreased, then they did not receive trastuzumab. After the standard dose of 240 mg/m$^2$ was administered, 7% of patients could not receive trastuzumab. This data corresponds almost perfectly with the Swain study data.

Three years ago the Surveillance, Epidemiology, and End Results (SEER)-Medicare database was queried for heart failure events in women between the ages 66 and 70 who were treated for non-metastatic breast cancer. The study was large and, despite its limitations, provided valuable data. Three subgroups of women were examined: those who had no adjuvant chemotherapy, those who had adjuvant anthracycline chemotherapy, and those who had adjuvant non-anthracycline chemotherapy. The incidence of new heart failure was determined by ICD-9 codes—intuitively we know this will be an underestimate across all three groups. The number of echocardiograms (ECHOs), MUGAs, and cardiology visits were used to try to answer “Are patients being screened appropriately?” From the three groups, those patients with the highest rate of heart failure were
those who received adjuvant anthracycline chemotherapy. Those with the least amount of ECHOs, MUGAs, and cardiology visits were the anthracycline chemotherapy group. None of these patients started off with metastatic disease and, perhaps even more amazingly, the number of ECHOs and MUGAs performed was zero in most patients—the least likely to be performed if patients received an anthracycline. This data is all from Medicare claims, yet it points back to the issue of 250 mg/m² being the threshold for the current recommendations.

Trastuzumab’s story is different because when the clinical trial was published, there was a high rate of heart failure with clear recommendations for monitoring. It is standard practice to have Q3-month monitoring of LVEF for patients on trastuzumab. This toxicity is well known among oncologists and is probably more in line with the real rate. If the LVEF drops, then implement the American College of Cardiology and American Heart Association (ACC/AHA or ACCHA) guidelines for Stage B heart failure/asymptomatic LV dysfunction. The guidelines include Class-1 indicated therapy with beta-blockers and ACE inhibitors and Class-2A indicated therapy of angiotensin receptor blockers (ARBs) for patients who cannot tolerate ACE inhibitors. There are no recommendations for treatment specifically for chemotherapy-induced cardiotoxicity, yet plenty of research to believe this therapy should be implemented.

All patients, limited to those who had ECHOs performed before and after the start of therapy, treated at Stanford from October 2005–October 2007 with either anthracyclines or trastuzumab were reviewed. A cohort of patients who had a significant LVEF drop to below normal was identified and compared to cohort who underwent MUGA. The purpose was to determine if patients being treated with cardiotoxic cancer therapies in which LVEF drops occur receive guide-
line-indicated therapies or cardiology consultation. The two most common cancer diagnoses in this study population were breast cancer and acute myelogenous leukemia (AML), yet other cancers were present. One might say, “We’re looking at AML patients. These were sick patients who were otherwise going to die.” We limited this to patients where the studies were performed in outpatients, carefully reviewed their files, and excluded anyone who had baseline hypertension or contraindications to any therapy. Standard doses of anthracyclines and trastuzumab were administered and the mean dose of doxorubicin was around 240 mg/m². The patients that received ACE inhibitors and/or ARBs, beta-blockers, and were referred for cardiology consultation were identified (Figure 4). Only 30-40% of patients that developed asymptomatic LV dysfunction diagnosed via ECHO ordered by the oncologist got referred to a cardiologist and were started on ACE inhibitors or beta-blockers.

Why do we run into these problems? Let’s pose a clinical scenario. We have a 50-year-old man with renal cancer/renal cell carcinoma and he enrolls in a clinical trial of a promising new therapy called “Lenihananiib”. The investigators are responsible and build prospective cardiac monitoring into the trial. The patient has a pretreatment LVEF that is normal at 60%, yet post-treatment it decreases to 35%. The patient is now deemed “asymptomatic from a cardiac standpoint” (even though he might be symptomatic) and his symptoms of fatigue or edema are written off as either being due to the malignancy or as a non-cardiac side effect of therapy. How should the oncologist grade this event according to The Cardiovascular Toxicity Grading (CTCAE) 4.0? The oncologist turns to CTCAE 4.0, opens up the index, and finds cardiac disorders. Must be the right place to look because right there is “left ventricular systolic dysfunction”. This sounds exactly like what was found—a drop in LVEF from 60% to 35%—yet there is nothing to treat unless it is symptomatic, so this patient’s cardiac dysfunction is grade zero and it is not reported. If the oncologist had turned to “heart failure”, then they would find this patient actually has a grade one event—an asymptomatic cardiac imaging abnormality. For those who are not oncologists and are not familiar with how seriously grade-one events are taken, here are some examples of grade two events for comparison—hypertrichosis, watering eyes that require non-operative intervention, and moderate flatulence. Though these may be important, a drop in LVEF from 60% to 35% is much more important than all three of these combined. If the oncologist had turned to “Investigations,” then they would find a listing for “ejection fraction decrease.” Now as a cardiologist, I do not understand the difference between left ventricular systolic dysfunction and a LVEF decrease, but there it is and it is listed as a grade three. The dilemma is this: Is the oncologist going to call this patient’s cardiac dysfunction a grade zero event and not report it at all? Call it a grade one? Or call it a grade three? Would you know what to do?

Here is an example of the confusion and how it can lead to real events. Sunitinib was approved for the treatment of gastrointestinal (GI) stromal tumors and renal cell carcinoma. Two sunitinib studies were published around the same time—the first investigated sunitinib versus placebo’s effect on GI stromal tumors with cardiac monitoring at baseline, day 28 of each
treatment cycle, and conclusion of the study. Sunitinib therapy was so effective that the trial got stopped early—the median number of cycles that patients received was two. Cardiotoxicity could have been missed because patients had not received it long enough. The study report states, “We noted no evidence of systemic mean decrease on LVEF. No patients were reported to have had clinical evidence of CHF.” If oncologists read this, then they may conclude that cardiotoxicity is not an issue with this agent, yet that is not the reality of the trial. The prescribing and labeling information on sunitinib (Sutent®) states, quoting the data from the Lancet study, that “11% of patients on sunitinib versus 3% on placebo had treatment-emergent LVEF values below the lower limit of normal.” (www.pfizer.com/files/product/uspi_sutent.pdf) Three patients on sunitinib had grade three (CTCAE 3.0 grading)—symptomatic heart failure reductions in LV systolic function to a LVEF less than 40%. Two of these patients died without receiving further study drug. No placebo patients exhibited any drop in LVEF. In the published study, no patients were reported as having heart failure, yet here in the drug monograph the same patients had a decrease in LVEF.

The second study investigated sunitinib versus interferon’s effect on renal cell carcinoma. Patients were excluded if they had “inadequate cardiac function” and the median duration of treatment was six months. There was a decline in LVEF for all grades—10% of patients with sunitinib and 3% with interferon. This may be a signal that there is something going on here. When reviewing the sunitinib (Sutent®) prescribing and labeling information in reference to this study regarding rates of decline in LVEF, 21% of patients with sunitinib and 12% with interferon. This can be explained—one group was using actual data while the other was using case report forms from the oncologist. Regardless, it is deceptive to say that there are no cardiac events with sunitinib.

In conclusion, guideline-based therapy is not occurring frequently enough in patients with asymptomatic LV dysfunction. One reason is the confusing semantics that need to be simplified. Asymptomatic LV dysfunction must be taken seriously and there needs to be a consistent reporting system for it. The first step is to fix CTCAE to be consistent and understandable, so we know there are real consequences when we miss real events.

References
Molecular Basis of Cardiotoxicity May Lead to Cardiovascular Drug Development
Aarif Y. Khakoo, MD, MBA

“Understanding the mechanism of toxicity of sunitinib may have a lot of significance in terms of toxicities of similar drugs with similar targets. This knowledge may have broader implications into how cardiologists and oncologists balance the critical ratio of efficacy to toxicity in cancer therapy.”

—Aarif Y. Khakoo, MD, MBA

Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor, whose targets include the vascular endothelial growth factor (VEGF) receptor, platelet-derived growth factor (PDGF) receptor, and C-kit. This drug has changed the landscape for patients with metastatic renal cell carcinoma because it was the first drug to show substantial efficacy in terms of progression-free disease and overall survival in these patients. Sunitinib is also FDA-approved for imatinib-resistant gastrointestinal (GI) stromal tumor. There are some emerging indications that it may have some significant benefit in hepatocellular carcinoma also.

Unfortunately, left ventricular (LV) dysfunction occurs in up to 20% of sunitinib-treated patients, with severe LV dysfunction occurring in up to 8% of treated patients. The sunitinib cardiomyopathy typically occurs within two months of drug initiation and is associated with substantial hypertension. It is reasoned that cardiomyopathy due to sunitinib and other tyrosine kinase inhibitors that inhibit PDGF, such as imatinib, may be indicative of a previously unappreciated role of cardiomyocyte PDGF-receptor signaling in the heart stress response. In support of the above reasoning was a recently published study in which cardiac-specific PDGF receptor-beta knockout mice were exposed to pressure overload stress and they developed profound LV dysfunction, a severe dilative cardiomyopathy phenotype to be exact, compared to controls. Mechanistically, we found that cardiac-specific PDGF receptor-beta knockout mice exhibited impairment in load stress-induced coronary angiogenesis and coronary microvascular dysfunction. This was a myocyte-specific knockout that develops an angiogenic phenotype in the heart.

Based on a number of experiments, we believe that this receptor regulates the paracrine angiogenic capacity of cardiomyocytes and that the cardiomyocytes have a critical contractile role. Emerging data from our group and others suggests that the cardiomyocyte itself plays a key role in producing factors that stabilize the coronary microvasculature, both under steady state conditions and when there is an increased substrate demand in the heart, such as hypertension.

Having established this, what is the mechanism of cardiomyopathy due to sunitinib, with the subtext of asking to what extent do sunitinib-treated mice resemble our PDGF receptor-beta cardiac-specific knockout mice? When we give sunitinib (in the same doses that were used in pre-clinical efficacy studies) to mice, there is a small, yet significant, decrease in LVEF. This is similar to what was seen in the PDGF receptor-beta knockout mice—sunitinib caused an impairment in coronary flow reserve and coronary microvascular function. We can measure this non-invasively,
using a special ultrasound probe that we had custom built for this indication, and invasively, using isolated hearts in which coronary flow in response to the vasodilator adenosine is measured. The sunitinib-treated hearts have markedly impaired coronary flow in response to vasodilator stress compared with the control. We also discovered that sunitinib induces impairment of the cardiac stress response in the same way that the PDGF receptor-beta knockout mice do. We measured cardiac contractile reserve, which is maximal pressure output from the heart in response to dobutamine, and found that sunitinib-treated mice have a substantial reduction in contractile reserve. The mice also developed significant LV dysfunction associated with an impaired cardiac angiogenic response (number of blood vessels per cardiomyocyte) when they were stressed with our pressure overload model and vascularity doubled. We observed a marked inhibition of PDGF receptor phosphorylation and expression in the heart in response to stress with sunitinib as well. The main point is to understand the cardiac dysfunction and severe coronary flow reserve abnormalities in sunitinib patients, not stress models. Biochemically, in sunitinib-treated patients we measured total nitrites in the heart, which is a rough readout of nitric oxide synthase function, and there is a marked reduction of nitrites. This suggests that the drug may be affecting the cardiomyocyte and its production of nitric oxide specifically, which may be relevant to the phenotype we observed.

To test this theory, isolated cardiomyocytes were exposed to lipopolysaccharide stress, which is a model of stress that induces upregulation of inducible nitric oxide synthase and also induces marked upregulation of phosphorylation of what we think is the relevant target in the heart of sunitinib PDGF receptor. When we treat with sunitinib, there is a marked reduction in inducible nitric oxide synthase upregulation, marked reduction in phosphorylation of the receptor, and a substantial reduction in nitrites produced by isolated cardiomyocytes, suggesting that nitrites may affect the paracrine angiogenic capacity of cardiomyocytes that is inhibited by sunitinib. Other data shows that sunitinib induces an endothelial-dependent and endothelial-independent coronary microvascular dysfunction. When we give acetylcholine, which is an endothelial-dependent coronary vasodilator that works by inducing nitrous oxide production in endothelial cells causing coronary vasodilatation, sunitinib-treated mice have an impairment in flow reserve with the non-invasive or isolated heart measurement. When we gave exogenous nitrates and sodium nitroprusside, an endothelial independent stimulus of coronary vasodilatation, we were unable to rescue coronary flow abnormalities in sunitinib-treated hearts. This suggests there may be structural abnormalities that result from sunitinib treatment that lead to impaired coronary microvascular function and subsequent cardiac dysfunction that may be very relevant to what our patients experience.

What kind of structural abnormalities could there be? The PDGF receptor signaling appears to regulate vascular pericyte function. Pericytes are small cells around vessels that appear to have both a contractile function and potentially a very important nutritive function for the microvasculature. In knockout animal models, pericyte loss occurs during development. In tumor genesis, PDGF appears to be an important regulator of pericyte growth. Pericyte abnormalities
may underlie the structural and functional abnormalities of sunitinib-treated mice. To test this, pericytes were measured and we found that pericytes are missing in these sunitinib-treated hearts. When we checked the control hearts, we observed that every vessel is covered by pericytes and in the sunitinib-treated hearts, pericytes are significantly reduced. There is a marked reduction of pericyte coverage in sunitinib-treated hearts compared with control hearts, yet pericyte coverage does not change in skeletal muscle for either group suggesting this is a myocyte-specific phenomenon.

To summarize, we found that sunitinib induces biochemical, structural, and functional abnormalities in the coronary microvasculature; impairs the cardiac response to stress; and sunitinib-induced coronary microvascular dysfunction may relate to PDGF receptor-dependent inhibition of cardiomyocyte paracrine function. This is our working model. We believe that sunitinib acts primarily on the myocyte, through the PDGF receptor, and potentially other receptors, to impair production of paracrine factors that maintain the normal crosstalk between cardiomyocytes, pericytes, and endothelial cells that act together to preserve cardiac contractile reserve. Disrupting this signaling here causes cardiac dysfunction and impaired cardiac reserve. Additional investigation of sunitinib-treated mice suggested that the pericyte abnormalities associated with sunitinib may cause cardiac dysfunction. To sort this out, we looked at thalidomide.

Thalidomide is an antiangiogenic drug and has an anti-VEGF signal, yet it actually appears to cause a maturation of vascular phenotypes. Whereas angiogenic developing and dividing vessels are not coated by pericytes, thalidomide in a dose-dependent way has been shown to enhance pericyte coverage of developing vascular networks and this may be very relevant to its antiangiogenic phenotypes. Consider the difference between a developing immature vascular network that is angiogenic versus a mature vascular network that is coated by pericytes—thalidomide appears to be pushing vascular networks to this more mature phenotype and it is possible that this may happen through other PDGF-dependent or independent processes.

Then we asked “What are the effects of thalidomide on sunitinib-induced cardiac dysfunction?” All the mice received sunitinib, some received the vehicle control (thalidomide + sunitinib), and some got a low dose of thalidomide. In this experiment, thalidomide prevented sunitinib-induced cardiac dysfunction during and after drug treatment. When we stopped sunitinib, even in the control-group of mice, they all got better and that is consistent with our collective clinical observations that at least until you reach some sort of critical tipping point, if we stop sunitinib in patients who develop LV dysfunction, they tend to recover. Therefore, thalidomide protects from sunitinib-induced cardiac dysfunction and coronary flow abnormalities. We can show that thalidomide attenuates sunitinib-induced coronary pericyte loss, suggesting that thalidomide is acting directly to stimulate pericytes and protect sunitinib-induced cardiac dysfunction. The thought is that thalidomide is acting downstream on the pericytes to protect against sunitinib-induced cardiac dysfunction.

Patients with abnormal coronary microvascular function may be the at-risk population for
developing sunitinib-induced cardiotoxicity; if you have impaired coronary flow reserve at baseline because of hypertension, renal failure, or atherosclerotic vascular disease, you may be the at-risk patient population who develop substantial flow reserve abnormalities when administered sunitinib, and in the face of stress, which is hypertension, you develop heart failure. This is consistent with the clinical observation that metastatic renal cell carcinoma patients with a history of coronary disease have an odds ratio of 18 of developing sunitinib-induced LV dysfunction. Furthermore, we believe that low-dose thalidomide is actually a promising cardio protective strategy for patients at high-risk for sunitinib-induced cardiotoxicity.

In conclusion, we are the first researchers to report any functional role for pericytes in the heart. We believe that acquired defects in coronary microvascular pericytes may contribute to both cancer therapy-induced and other forms of human heart failure. This topic is ripe for potential research as there is much more to discover.

References

PREDICT Trial: Prospective Point of Care Cardiac Biomarkers to Detect Cardiotoxicity
Daniel J. Lenihan, MD
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“The PREDICT trial has two goals. The first is to show that biomarkers are a more effective strategy than LVEF measurements or clinical follow-up for detecting toxicity. The second is to learn how big of an influence certain cardioprotective medicines have and with this being a large, multicenter trial, the cardiologists involved are going to make their own decisions about which medicine to use and then over time we will learn, in a non-randomized, observational fashion, which drugs are the most effective and which patients respond the best.”

—Daniel J. Lenihan, MD

The development of cardiovascular problems in cancer patients is something that needs to be addressed, so we can detect and treat optimally—this involves CTCAE criteria that we discussed earlier, which has limitations. One of the limitations is that the oncologists would have to grade the patient’s symptoms. In one study, patients undergoing chemotherapy were asked to report their symptoms, in addition to the physicians reporting their symptoms. Eight primary
symptoms during chemotherapy were investigated. The physician identified dyspnea only 23% of the time in this carefully-conducted study. If we base our toxicity on symptoms that are recorded, a vital piece of information may be missed. Overall, the physicians recording the symptoms were only sensitive to them about half the time; therefore, basing toxicity solely on symptoms is not going to be adequate. For example, to diagnose heart failure, the classic triad of symptoms is dyspnea, lower extremity edema, and fatigue. These are also symptoms that patients suffer when they are undergoing chemotherapy. Making an accurate diagnosis can be challenging—detecting the changes and then deciding if those changes are a real event or not is where biomarkers have a role.

Biomarkers (e.g., troponin, b-type natriuretic peptide [BNP], N-terminal BNP) used in cardiology are also used in oncology and are clearly an important adjunct in our diagnosis. In a study looking at BNP guided therapy over the course of treatment for heart failure, cardiologists are assessing the patients so they should be able to figure out symptoms or physical findings. Even with this knowledge, the group that had BNP-guided treatment had fewer cardiac events and a better reduction in either heart failure or death during the course of the study. The BNP added something to the overall picture just as Dr. Cardinale showed the troponin added something during chemotherapy.

Ewer and colleagues reported that when patients developed cardiac toxicity during trastuzumab therapy, and had focused treatment of their heart failure, their heart function was more likely to recover. Trastuzumab therapy could continue without a recurrence of heart failure and this would allow the patient to receive optimal treatment for their cancer. This recovery may not only apply to trastuzumab, yet could apply to other treatments where cardiotoxicity is detected. Cardinale and colleagues point out that early diagnosis is critical. If the problem was detected in the first six months, the chance of improvement was quite good. If the problem was not detected until six months or later, then there was no real benefit. This is not a new concept for cardiologists, especially regarding the model for ischemia. If someone has an acute myocardial infarction, then we need to treat at the earliest phase in order to be more successful because “time is muscle.” To apply this same thinking—detection of cardiotoxicity is a crucial point.

Recovery is more successful when cardiotoxicity is detected early. For example, it has been proven that if we treat these patients with ACE inhibitors, they are likely to improve and if we don’t treat them, they are not likely to improve. Carvedilol also appears to be cardioprotective. In patients not receiving carvedilol, there was a significant drop in LVEF during treatment with chemotherapy. These studies emphasize that early detection is key.

The next question is which patients should be treated? Should every patient be treated or just the ones in which we identify as high-risk, or that have developed a toxic signal? If you reviewed the AHA, ACC, HFSA, and ASCO Web sites, the best advice out there in terms of guidelines is that there should be a baseline LVEF measurement and a repeat of that measurement at some time interval to be determined, symptoms are the mainstay of heart failure diagnosis, and there are no
recommendations for biomarker testing or preventative therapy. The LVEF measurement by itself is not a good indicator of outcome or heart failure condition since approximately half of patients admitted to the hospital for heart failure have a normal LVEF and their prognosis is similar to those with systolic dysfunction.

In a pilot study conducted at MD Anderson to demonstrate the role of cardiac biomarkers, cardiac risk factors were common in the study population—50% had hypertension, 20% had a family history of early heart disease, more than 30% had hyperlipidemia, more than 30% were obese, and more than 10% were active smokers. This is the average population of a cardiology clinic, yet these patients were being treated for cancer with a high likelihood of underlying heart disease prior to treatment. By examining many study parameters it was clear that the only factors that were significantly associated with cardiac toxicity were advanced age, a history of myocardial infarction, and an elevated BNP. If a patient had a BNP >200 pg/mL, then they had 44 times the risk of developing cardiotoxicity during chemotherapy compared to those without BNP elevations and this was much better at predicting cardiotoxicity than LVEF changes were. Out of the 11 that developed cardiotoxicity, 7 had normal serial LVEF measurements. This indicates that the current standard is missing quite a bit. The accuracy of the test for predicting cardiac events was reviewed before we started this study. A BNP >200 was chosen because of better test characteristics in the elderly population and a population with multiple comorbidities with the test cutoff at 100. The BNP >200 test was 91% sensitive and 90% specific with a very high negative predictive value. If a patient underwent chemotherapy and their BNP stayed under 200, then they had almost no chance of developing toxicity. A BNP elevation sometimes occurred on the day that patients developed a problem or many days before a clinically evident problem. Many BNP elevations also occurred a long time before the patient developed a toxic event. The only patient that did not have a BNP >200, who developed a symptomatic arrhythmia, had only gotten one cycle of chemotherapy and he also had severe COPD. We believe that the test still detected an abnormality, yet at our preset cutoff was not quite as elevated.

The rationale of the PREDICT study, which is a multicenter trial, is that troponin and BNP biomarkers are reliable, non-invasive, and simple to measure. In addition, early identification of LV dysfunction would stratify patients needing adjustments in their chemotherapy or who may benefit from concurrent use of cardioprotective agents (e.g., ACE inhibitors, beta blockers). The inclusion criteria are patients between the ages of 18 and 85, starting a new course of chemotherapy that includes an anthracycline (does not have to be first-line therapy and previous anthracycline use is allowed), and has a life expectancy of >1 year. Exclusion criteria are patients with unstable angina or myocardial infarction within three months of registration; a LVEF <50%; receiving concurrent dexrazoxane (because this drug is a potential cardioprotectant and appears to decrease the incidence of troponin release); decompensated heart failure in the last three months prior to registration; pre-existing or prior symptomatic arrhythmia (within three months); severe pulmonary disease (FEV<1 L), and/or pulmonary hypertension (mean pulmonary artery pressure >/=60
mm Hg), and/or dependent use of oxygen; and BNP >/= 200 pg/mL or troponin >/= 0.4 ng/mL at baseline (abnormal biomarkers at baseline indicate cardiac problems already).

The cardiac events shall be defined as any new symptomatic cardiac arrhythmia, acute coronary syndrome, symptomatic heart failure, development of asymptomatic left ventricular dysfunction (defined as LVEF reduction of 10% to <50% or a decrease >15% from baseline), and sudden cardiac death (defined as rapid and unexpected death from cardiac causes with or without known underlying heart disease). BNP and troponin shall be checked by a point-of-care test (performed at any oncology office or treatment center) prior to chemotherapy. If the level is abnormal to mild or moderate level, the cardiology team shall provide input. If the markers are elevated to a significant level, then a formal cardiology consultation will be requested.

In conclusion, the ability to predict and identify patients who develop cardiac toxicity with chemotherapy needs improvement. Biomarkers may actually identify those patients long before heart failure is present. Establishing a method to easily and reliably detect cardiac toxicity will have a profound impact on outcomes.

References
Neuregulin in Heart Failure: An Upstream Effect of ERB2 Signaling
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“The biology of neuregulin and ErbB2 signaling is essential for the heart and has prompted us to question whether or not they could be used as therapy in heart failure.”

——Carrie A. Geisberg, MD, MSCI

In 1998 the FDA approved trastuzumab for the treatment of HER2-positive breast cancer; however, it became apparent that concurrent administration of anthracyclines with trastuzumab increased cardiotoxicity four-fold. What sort of biology was causing this increased cardiotoxicity? Let’s look at the different ErbB receptors (e.g., ErbB1, ErbB2, ErbB3 and ErbB4).

ErbB2, a non-ligand or orphan binding receptor, is special because it tends to be over-expressed in breast, ovarian, gastric, and salivary cancers, yet is also present on heart tissue. ErbB2 requires heterodimerizing with various receptors, such as ErbB4, and neuregulin will bind to the ErbB4 receptor. ErbB2 will then undergo a conformational change and will allow the heterodimerization of these receptors that produces downstream signaling which is important. There could be some problematic issues if you are blocking this receptor activation of the heart.

Neuregulins are a family of four structurally-related proteins that are part of the epidermal growth factor (EGF) family. Neuregulins are expressed in several different tissues, share a common EGF domain, and have a transmembrane portion on the cytoplasmic tail. They are important because these proteins help regulate growth differentiation and survival in different tissues such as breast, epithelial, glial, neural, skin and endothelial, and cardiac myocytes. Neuregulin is expressed on the endothelial cells in the heart. It becomes activated by a particular stimuli (e.g., physiologic stress, ischemia, or exercise) which will have a metalloproteinase actually cleave to the neuregulin from the endothelial cells, to then act upon the cardiac myocytes through the ErbB4 and ErbB2 binding, and have downstream survival and pro-growth signaling. Is neuregulin actually needed for cardiac development? An ErbB3 knockout mouse model was created to look at the embryologic development of neuregulin. Embryologically the heart is a tube-like structure that will begin to fold upon itself and have trabeculation and endocardial cushion formation, which forms the AV valves anywhere from day 9 1/2 to day 10 1/2. When you have an ErbB3 knockout mouse, they tend to die in utero because they have normal trabeculation, yet fail to form the normal AV valves. If you had an ErbB2 or ErbB4 knockout mouse, the heart fails to form normal trabeculation, yet will have normal endocardial cushion formation. If you have a neuregulin or ErbB2 signaling that is knocked out, trabeculation and endocardial cushion development will fail. Therefore, neuregulin is critical for cardiac development.

What is the role of neuregulin-ErbB signaling in the post-natal heart? A conditional knock-
out experiment was undertaken in mice where investigators blocked the ErbB2 receptor. A thin, dilated left ventricle develops, which when compared to controls, is very abnormal, yet this was the similar phenotype that we saw with trastuzumab. This very abnormal looking cardiac myocyte structure has increased vacuoles and increased mitochondria, thus showing that neuregulin plays a role in helping maintain cardiac myocyte integrity, even in the post-natal heart.

Can neuregulin be protective? Can it help prevent cardiac damage that is related to toxic exposure? An ex-vivo experiment where neonatal rat ventricular myocytes were treated with daunorubicin for 24 hours was undertaken. The cardiac myocytes became very sick and distorted from their normal structure. If these cells are pretreated with neuregulin for 30 minutes, they are a lot less distorted and tend to maintain their normal architecture. When you look at the TUNEL staining for the number of apoptosis, there are fewer cells that became apoptotic. This suggests that neuregulin has some protective effect against certain toxic exposures, yet the exact intracellular mechanism is not known.

What happens to human circulating neuregulin levels when exposed to anthracycline? One published data set had 16 women undergoing breast cancer chemotherapy and a baseline level of neuregulin compared to a level after anthracycline exposure. There was a significant drop in their neuregulin levels post-anthracycline exposure. Similarly, a larger published data set shows that in comparison from pretreatment, mid-treatment, and post-treatment, neuregulin levels fall throughout chemotherapy. The translational potential of neuregulin and ErbB2 signaling in the heart is important to help the cardiac myocyte to develop and maintain its structure. Can we actually think that neuregulin can be used as a therapy?

Lui and colleagues wanted to see if neuregulin was cardio-protective and if it could be used therapeutically in different forms of cardiomyopathy. They first looked at an ischemic cardiomyopathy model where they took rats and ligated the left anterior descending coronary artery. Then they investigated a drug-induced form of cardiomyopathy where they expose these rats to doxorubicin and a viral-induced cardiomyopathy where they exposed them to coxsackie. In the ischemic model of cardiomyopathy, there was an early MI group and a late MI group. The rats in the early MI group received treatment with neuregulin beginning 7 days after their MI and continuing for either 5 or 10 days. The left ventricular ejection fraction (LVEF) did improve with neuregulin treatment. The late MI group began treatment with neuregulin for either 5 or 10 days two months after the infarct. There was a slight improvement in LVEF, yet it is not nearly good as with an earlier treatment of neuregulin. It is great that the LVEF improves with treatment of neuregulin, yet does it actually have any survival benefit in this ischemic cardiomyopathy model? The investigators decided to look at the effects of vehicle versus captopril versus recombinant neuregulin plus recombinant neuregulin plus captopril. The recombinant neuregulin did seem to have a survival benefit over just captopril or vehicle alone. Looking at the different models, particularly the drug-induced model, investigators treated with doxorubicin for 4 weeks versus when they pretreated it for 7 days and these
cardiac myocytes looked more similar to those of the control. In the viral-induced cardiomyopathy, these rats were exposed to the coxsackie virus, and there is an increase lymphocytic infiltration versus when they were pretreated with neuregulin where there is a decrease in the lymphocytic infiltration. This is tremendous preclinical data, yet what happens in humans?

Jabbour and colleagues (American Heart Association, 2009) performed a single center, prospective, nonrandomized open-label study in humans, the first human study, with recombinant neuregulin.5 Keep in mind that this is an EGF domain-only, short-acting type of recombinant neuregulin and in healthy individuals it is undetectable after 45 minutes. Their study population consisted of New York Heart Association (NYHA) Class II to Class III patients with an LVEF <40 % (n=15). This group was on optimal medical therapy with ACE inhibitors, beta-blockers, and diuretics. Patients had no implantable cardioverter defibrillators. A first-time dose of recombinant neuregulin of 1.2 mcg/kg was infused over six hours—this one-time infusion was used to assess acute hemodynamics and tolerability. For study days 2 through day 11, investigators conducted a dose-finding investigation with a 12-hour infusion where they took 0.6, 1.2 and 2.4 mcg/kg and assessed hemodynamics with a pulmonary artery catheter at day 1 and day 12. They followed up with patients at 4, 8, and 12 weeks. Their endpoints were safety and tolerability, and they looked at LVEF, end-diastolic and systolic volume by MRI, acute and chronic hemodynamics, and some neurohormonal markers. During the six-hour infusion with the recombinant neuregulin, there is no significant fall in cardiac output. There was a little bit of improvement in cardiac output that corresponded with increase in heart rate and increase in stroke volume. Investigators did not see any significant drop in mean arteriole pressure or any significant hypotension, which was positive. When they tried to see if there were any sustained hemodynamic properties, they did not find anything statistically significant. The only thing they found was a slight increase in mean arteriole pressure from 88 to 84, which is probably not clinically significant.

Reviewing the sustained results, patients had a small increase in LVEF from 32 to 36% and a small decrease (9% reduction) in left ventricular and systolic volume, yet safety was still a major concern. There were two serious adverse events: nausea and vomiting in a patient caused termination of the drug at day nine and another serious event of nausea and vomiting required an extensive hospital workup with a CT of the abdomen, ultrasound, and esophagogastroduodenoscopy. One patient also had a mild echocardiogram (ECG) and ECG changes in troponin elevation and one patient noted a basal squamous cell skin cancer. Overall, it was concluded that recombinant neuregulin for 11 days was well-tolerated and relatively safe. This data was not sufficient for dose-finding purposes of the trial.

Phase II of this study was conducted at five medical centers in Beijing. It was a randomized control trial of recombinant neuregulin (EGF domain only, recombinant neuregulin). The patient population (n=44) consisted NYHA Class II to III and LVEF less than 40% randomized to treatment or placebo groups for 10 days. They were given 0.3, 0.6, or 1.2 mcg/kg infused over 10 hours versus placebo. Primary endpoints were changes in LVEF and changes in systolic and
diastolic volume by MRI at days 11, 30, and 90. Results showed there was a change in the LVEF only at the 0.6 mg/kg dose and this was showing an improvement from days 11, 30, and up to 90. There was also a significant decrease in the end-systolic and end-diastolic volumes at 30 and 90 days. The investigators concluded some improvement in the overall LV remodeling. They did not see any changes in secondary endpoints—quality of life, six-minute walk, or NYHA class.

In conclusion, coming soon is a Phase 1A, 1B study with recombinant neuregulin and heart failure that has been developed in collaboration with Acorda Therapeutics. This study is with a different form of recombinant neuregulin where it has an EGF domain and a kringle-like domain, which is more similar to the natural occurring neuregulin in our bodies. This recombinant neuregulin is also known as GGF2. By having the kringle-like domain, it circulates longer in the system more like what we would observe clinically. Phase 1 will be a single-dose, randomized, double-blind control dose escalation study and will be the first study in man with GGF2 and the first study in the U.S. where recombinant neuregulin has been used. There has been a collaborative effort between Vanderbilt, Acorda Therapeutics, and NIH to determine the safe, tolerable, and most biologically effective dose of GGF2. The plans are to commence the study in late fall.

References
Multicenter Registry for CV Events During Cancer Therapy
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“Areas for growth include, expanding data collection to all disease groups receiving cardiotoxic medications; building a consortium of national and international sites; and building a consortium of pediatric, young adult, and adult survivors.”
—Bonnie Ky, MD, MSCE, FACC

Cardiotoxicity with cancer therapy is a substantial health burden. Doxorubicin-induced heart failure has a poor prognosis (hazard ratio of 3.5 fold) as compared with idiopathics. In breast cancer, more than 2 million adult survivors in the U.S. alone are believed to be at risk for cardiotoxicity. Pediatric cancer survivors have a considerable long-term risk of cardiac disease—elevated risk of heart failure and coronary disease in survivors (relative risk approximately 10-15) and an increased late risk of cardiac mortality.

The landscape of cardiotoxicity continues to grow with anthracyclines, platinum-based therapies, monoclonal antibodies, and tyrosine kinase inhibitors (TKIs) having extremely unfavorable cardiac effects. Cardiotoxicity is not just about LV dysfunction and heart failure, it also includes arrhythmia, ischemia, thromboembolism, and hypertension (Table 3). It has

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**Table 3. The Landscape of Cardiotoxicity Continues to Grow**

- Anthracyclines, platinum-based therapies, monoclonal antibodies, and tyrosine kinase inhibitors have unfavorable cardiac effects.
- Cardiac toxicity includes: LV dysfunction, heart failure, arrhythmia, ischemia, thromboembolism and hypertension.

<table>
<thead>
<tr>
<th>Cardiotoxic Effect</th>
<th>Agent</th>
<th>Incidence (%)</th>
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</thead>
<tbody>
<tr>
<td>LV Dysfunction</td>
<td>Doxorubicin</td>
<td>3.26</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>7.28</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td>2.28</td>
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<tr>
<td></td>
<td>Sunitinib</td>
<td>2.7-11</td>
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<tr>
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<td>5.47</td>
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<tr>
<td></td>
<td>Sorafenib</td>
<td>17.43</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>4.35</td>
</tr>
</tbody>
</table>

Adapted from Yeh ET al. J Am Coll Cardiol. 2006;53:2331-47.
already been stated that the current methods for identifying high-risk patients remain very limited. Currently, we are using left ventricular ejection fraction (LVEF) assessment via echocardiogram (ECHO) or multi gated acquisition scan (MUGA) as a main modality. The limitations here exist in the ability to detect early changes or adequately predict late declines in LV function, LVEF is highly load-dependent, and interobserver variability. To identify the risk of other cardiotoxicities we are using a routine clinical cardiac history and physical as the main modality. There remains a critical need to develop robust methods to identify high-risk individuals. Significant advances, such as the utilization of troponin-I in identifying patients at high-risk for developing cardiotoxicity in cancer therapy3-5 and understanding of the basic science mechanisms that suggests trastuzumab cardiotoxicity may be related to ErbB2 inhibition and so forth, have added to our body of knowledge, yet there remains a critical need to continue to move translational research forward.6 There are gaps existing in translational medicine in the application of our basic science knowledge, the identification of high-risk patients, and mechanistic pathway-based biomarkers in order to improve our understanding of the disease process and our ability to risk-predict.7 To accomplish these goals, multi-institutional consortiums are absolutely necessary to test these hypotheses.8 This represents a very unique opportunity to unify and advance the field of cardio-oncology with an increase in sample size, a standardized approach to data collection and outcome assessment, and the ability to have long-term follow up.

At the University of Pennsylvania (Penn), we have a Penn Heart Failure Study (PHFS) cohort whereby patients are diagnosed with heart failure at point X and subjects are subsequently enrolled. Baseline data includes a bank serum sample, plasma and DNA, a 2D ECHO, and detailed clinical covariant. Patients are followed every six months via questionnaire and clinical follow-up. The following outcomes are adjudicated: all-cause death, cardiac transplantation, and ventricular access device placement. This cohort is used to answer translational research questions that we believe are important and of major interest. In regards to neuregulin, we asked “What is the relevance of circulating neuregulin in humans and in chronic human heart failure?” In collaboration with Penn, Doug Sawyer measured neuregulin levels in approximately 900 PHFS subjects and found that neuregulin is a marker of heart failure severity in patients with Class IV heart failure having significantly higher levels as compared to Class I.9 Those patients in the first quartile, neuregulin-1ß, had significant increased risk of death or transplant compared to those patients in the fourth quartile with an unadjusted hazard ratio of almost 1.8.

The PHFS cohort has also been used to answer other research questions. It has served as an invaluable resource to gain insight into biomarkers, genetic variation, and cardiac remodeling in human heart failure. We have used this cohort to measure SV2, pro-BNP, and vascular growth factors, yet how do we continue to move forward in cardio-oncology? We believe through a prospective, multi-institutional consortium whereby there is a shared data repository, we can identify clinical risk factors that are important in cardiotoxicity; in the field of oncology develop the circulating biomarkers that are important in risk assessment, diagnosis, genetic susceptibility, sensitive
ECHO indices of cardiac function, uniform outcomes with long-term follow-up; and improve the quality of care of these patients.

To conclude let me explain a study we have underway at Penn. We have initiated the Cardiotoxicity of Cancer Therapy Cohort Study to determine baseline and longitudinal associations between biomarkers and the risk of adverse cardiovascular outcomes in patients exposed to cardiotoxic agents. The inclusion criteria are age 18 years or older with breast cancer receiving an adjuvant or neoadjuvant regimen that is potentially cardiotoxic. The exclusion criteria are pre-existing myopathy with an LVEF <50 % or any contraindication to chemotherapy. This currently exists as a single site, single disease group study at Penn. Patients are recruited through new visits at the Breast Cancer Center, identified via a medical chart review, and then referred from oncologists—this collaboration is absolutely necessary. The patients that have been recruited thus far are those primarily receiving doxorubicin, trastuzumab, or a combination of the two agents. The target has been to recruit at least two new patients each week.

In regards to the overall study design, patients in the anthracycline and trastuzumab group will receive doxorubicin and cyclophosphamide for four cycles, then trastuzumab (for one year). Blood samples and a questionnaire/outcome assessment are obtained at baseline and every six weeks. From the blood sample, DNA is being isolated and we are banking plasma and serum. Patients will undergo an ECHO at baseline and every three months. Patients in the trastuzumab without anthracycline group (trastuzumab given for one year) will have a blood sample drawn and questionnaire/outcome assessment at baseline and every six weeks and an ECHO at baseline and every three months. Patients in the anthracycline without trastuzumab group receives doxorubicin and cyclophosphamide for four cycles, then paclitaxel. Blood samples are drawn at baseline and then approximately every six weeks, then at the completion of the anthracycline chemotherapy, again at the completion of all chemotherapy, and then following one year after doxorubicin. An ECHO is obtained at baseline, the completion of chemo, and one year after doxorubicin. In terms of our assessment of exposures and outcomes, patients give a blood sample of 16 mL at baseline and 12 mL at follow-up—typically drawn prior to chemotherapy infusion by the nurse. The ECHO is completed according to a standard protocol on a GE Vivid 7 machine. We are obtaining additional 2D images at high frame rate and with tissue doppler for strain analysis. This adds about 15 minutes to the protocol. Blood pressure is also recorded at the time for ECHO to assess ventricular vascular function measures. All results are being archived for future quantitative analysis by the Penn Core Lab. The questionnaires provide detailed information regarding patients’ medical, social, and family history pertaining to breast and cardiac history. Basic physical exam parameters, including height, weight, blood pressure, and heart rate are noted. The MD Anderson Heart Failure Symptom Survey and the Godin Leisure Time Questionnaire, which is an assessment of overall exercise activity, are administered. The clinical data is being managed and stored by Velos eResearch, which has patient and study-level system architecture (compliant with all industry standards), a custom-specific data dictionary, and the capacity to support multi-institutional
studies. The biospecimens are tracked via a homegrown electronic database and the ECHOs are archived for future quantitative analysis.

References

Amyloidosis: A Disease All Cardiologists Should Know About
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“Cardiac biomarkers have turned out to be very useful for prognosticating patients with amyloid cardiomyopathy.”

— David C. Seldin, MD, PhD

Amyloidosis is a mysterious illness. What I am about to share is a patient story that was profiled in the Medical Mysteries segment of the *Washington Post* a year and a half ago or so. This patient is in the military and happens to be a very shy soft-spoken guy, yet he was very interested in talking to the Post because of the problems that he faced in terms of receiving a diagnosis of amyloidosis.
At the time his symptoms started, he was forty-seven, in the Marine Reserves, and a military historian. In late 2003, he had crushing fatigue and knew something was wrong, especially because he was used to running five miles a day with his wife and could no longer do that. At first he was diagnosed with exercise-induced asthma because of his dyspnea and fatigue. A couple of years passed while he saw various specialists in the Virginia area where he lived and finally there was some question of an abnormality on an echocardiogram (ECHO); however, nothing was done for a while longer. The possibility of an anxiety or other psychological component was also raised—this is a common thing that our patients, particularly women, tell us. As a few more months went by, his symptoms were getting worse and worse. He said, “I don’t know what I have, but I’m dying from it.” By this time he had developed fluttering in his chest and some signs of neuropathy. Finally, in October of 2005 at Johns Hopkins Hospital, because of his previous abnormal ECHO findings, he underwent an endomyocardial biopsy that revealed cardiac amyloidosis. He was referred to us at Boston University because we have a program with a longstanding interest in these diseases.

When he came to us, he still looked very good. He had mild orthostatic hypotension, yet none of the other classic signs of amyloidosis—macroglossia, periorbital ecchymosis, other bleeding or bruising, submandibular gland enlargement, hepatosplenomegaly. He did have an elevated jugular venous pressure with hepatojugular reflux, minimal basilar rales, and 2+ pedal edema. Laboratory studies at that time showed a gram of proteinuria and otherwise normal kidney and liver function. His ECHO at this point had a 14mm interventricular septal thickness, LVEF was normal with some diastolic dysfunction, and BNP was 161 pg/mL. He had a very subtle plasma cell dyscrasia in the marrow, a number of plasma cells that would not be considered to be particularly abnormal, but there was an excess of lambda-staining cells, suggesting that he had a clonal population hidden in the marrow. One of the things we teach our hematology colleagues is that serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) are not good screening tests for this particular disease because they are usually abnormal in multiple myeloma and in a low-grade plasma-cell process they are not. Immunofixation testing usually does show monoclonal proteins and we have a free light chain assay that is useful for plasma-cell diseases. Immunoglobulins are made up of heavy chains and light chains. When you have a plasma-cell dyscrasia in the marrow—amyloidosis or multiple myeloma—there is an excess of light chains produced and these can be measured in the blood through a standard available assay. It is a very sensitive and quantitative assay that allows us to monitor plasma-cell diseases. This patient’s lambda free light chain was two-fold above normal and the ratio of capita lambda light chains was also perturbed. This patient had no sign of an M spike on a SPEP, yet did have a little peak on a UPEP. When you stain these with specific antibodies against heavy and light chains, what you are able to detect in an immunofixation study is a lambda light chain band in the serum and an obvious one that everybody can see across the room in the urine. This patient does have a monoclonal protein or paraprotein production. In the marrow we stain for plasma-cell CD138 and kappa lambda. In this patient’s stain there is an excess of the brown staining peroxidase-positive lambda cells. In terms of cardiac studies, ECHOs will show...
a thickening of the ventricular walls. That’s usually a concentric hypertrophy and evidence of relaxation abnormalities in diastole. One important pearl is that the classic sparkly appearance on an ECHO is rarely seen anymore, so it should not be a requirement to make this diagnosis.

What is amyloidosis? As we said before, it is a mysterious disease that was actually described more than 150 years ago in the early days of microscopy by Virchow in Germany. It was fairly common in autopsies in a pre-antibiotic, pre-anti-inflammatory era for patients to have developed “secondary amyloidosis” (AA) from chronic infections and inflammation, which usually causes renal disease. In terms of cardiac involvement, the various forms of systemic amyloidosis (sporadic “primary” amyloidosis [AL] and senile systemic amyloidosis [SSA]) predominantly involve the heart. All of these diseases have unifying mechanisms where the protein precursors or peptides, derived from precursor proteins, form oligomeric aggregates through cross-beta sheet formation and then these seed massive polymers, that are 10 nanometers wide and can be hundreds of nanometers long in tissues, are seen by electron microscopy. We still use Classic Congo red staining, which will bind to any of these forms of fibrillar material and tissues and under polarized light turns that apple-green color, that is very specific to these protein deposition diseases.

The reason amyloidosis is challenging for diagnostics is the clinical presentation. Some patients have predominantly soft-tissue manifestations—a patient says their tongue is big and hard, then amyloidosis is what it is until proven otherwise. Patients can have joint problems—carpal tunnel syndrome is quite common. Kidney disease is usually proteinuria although some patients have primarily tubular deposits and will have renal failure without a lot of proteinuria. Patients can have GI symptoms due to either direct deposition into the GI tract or malabsorption or autonomic involvement causing GI dysmotility. Peripheral and autonomic neuropathy is common and a minority of patients can get bleeding problems, such as periorbital ecchymosis (also known as raccoon eye)—this should raise suspicion for AL-amyloidosis. Any of these symptoms alone are pretty nonspecific. The key is when we see patients that have symptoms involving multiple organ systems—we have to think about these diseases. With pure cardiac amyloidosis you really have to be looking quite closely and get a biopsy. The next step in making a diagnosis is to get a tissue biopsy demonstrating the presence of amyloid fibrils and that can be done through an involved organ—endomyocardial, kidney, or liver biopsies. It is common to perform a simple, useful, noninvasive bedside aspiration of fat from the abdominal wall and, depending on the type of amyloid, it is positive in 80-90% of patients. In addition, modern typing is dependent on a variety of biochemical and immunochemical techniques—immunoelectron microscopy and proteomic and mass spec techniques—that are required to make an accurate diagnosis.

In amyloidosis patients, cardiac disease is a major determinant of outcome regardless of the type. Dubray and colleagues investigated the survival of patients with symptomatic amyloid cardiomyopathy. The median survival was only about a year for untreated patients. In those days the overall survival for AL-amyloidosis was only about a year and a half because of ineffective therapies. These patients were dying because of massive infiltration of amyloid into the myocard-
dial walls. This tends to start in a perivascular distribution, yet can infiltrate the whole myocardium and can affect the conducting system also. In more recent research we have found that it is not only the infiltrative process that is the problem in the heart. Some patients with relatively modest increase in wall thickness and less amyloid deposition by biopsy actually have considerable myocardial dysfunction. Liao, Brenner, Shi and colleagues have researched mechanisms of cardiac dysfunction. In ex-vivo cell-based models, cells can actually take up light chains and induce signaling pathways that lead to oxidative stress and dysfunction of individual cardiomyocytes, as well as the heart. Learning more about these mechanisms will allow us to develop more effective targeted therapies in the future (Figure 5 and 6).

**Figure 5. Diagnostic Algorithm**

```
Amloid Heart Involvement

Screen for Plasma Cell Dismastia
Cardiac Only, Exclude SSA
Multiorgan Disease
See AL Treatment Algorithm

Screen for AF Mutations
Pos: Genetic Counseling
Neg: SSA?
Investigational Agents
Supportive Care

AF = atrial fibrillation, SSA = senile systemic amyloidosis, AL = primary amyloidosis.
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**Figure 6. Treatment Algorithm**

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AL CMP

Mild
HDM/SCT
Non-SCT Protocol

Severe
Significant Other Organ Disease
Limited Other Organ Disease

Oral Chemo
Eval for OHT

AL CMP = Primary amyloidosis Comprehensive Metabolic Panel, HDM/SCT = High dosage melphalan with stem cell transplantation, Non-SCT = No stem cell transplantation, OHT = orthotopic heart transplantation.
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The most common form of amyloid in the heart are AL or light-chain amyloid. If you believe amyloidosis is the diagnosis, look for evidence of a B cell or plasma cell disorder in the bone marrow and production of light chains in the circulation. If this cannot be found, then we have to think more about the various genetic forms or late onset forms of amyloid that are most commonly due to transthyretin deposition. There are a number of other abundant serum proteins that can form amyloid in tissues, yet transthyretin, also known as pre-albumin, is the most common one to be mutated and, in the absence of mutation, with age forms age-related or senile systemic amyloidosis that frequently involves the heart.

Once the culprit is identified, then treatment can begin. Patients with very severe cardiomyopathy are very intolerant of most of the chemotherapy agents, corticosteroids, and do not do well with standard heart-failure therapies. These patients either get mild oral chemotherapy regimens or can be considered for orthotopic heart transplantation. A key component to getting these patients through any kind of treatment and prolonging life is appropriate management of their heart failure—management of amyloidosis heart failure is quite different from standard heart failure treatment. Hearts loaded with amyloid deposits are intolerant of the negative inotropes and after-load reduction that is commonly used for managing heart failure in patients with systolic heart failure. In fact, there is a specific problem with digoxin where it binds to amyloid fibrils and causes very high and toxic local concentrations, even in the presence of appropriate systemic digoxin levels. Arrhythmias are a big problem with amyloidosis patients. Unfortunately, there is very little evidence-based guidance on how to manage the arrhythmia—antiarrhythmics (e.g., amiodarone), ablation of foci, and implantable defibrillators have been used. These methods do not work in all patients, especially with thickened myocardia as ventricular arrhythmias cannot be reversed with external or implantable defibrillation. Many of the patients have atrial fibrillation and poor atrial contractility because of the amyloid deposits in the atria and ventricles. Anticoagulation is needed even when they are in sinus rhythm. There is a growing menu of antiplasma-cell agents for treatment of these patients—chemotherapy, high-dose chemotherapy, immunomodulators, and proteasome inhibitors are all very useful drugs that come from the myeloma field and can be translated with some care into patients with amyloidosis. Many of these agents have unexpected toxicities in patients with amyloid cardiomyopathy. Before some of these newer agents were available, in 1994, we started treating patients with high-dose intravenous melphalan (because the standard oral dose was ineffective) supported by autologous stem-cell transplantation. It takes a year to give people an adequate antiplasma-cell dose of oral melphalan, and if you have a disease with a 6-12 month median survival because of progression of heart failure or other organ failure that is not going to work out very well. High-dose chemotherapy was used to more rapidly arrest production of light chains in the hopes that this would allow patients to have some improvement in organ function. Worsening of heart failure and arrhythmia is seen as well as other problems, yet carefully selected patients can get through this and our current treatment-related mortality is running about 5%. Some of the centers have reported mortality with this procedure as high as 30-40%, which is
not acceptable as an option for patients. Patients with a good hematologic response have a tremendously prolonged survival—the median may be more than ten years. Non-hematologic complete responders do not do as well. If they continue to make light chains, infiltration of the organs progress, and the disease worsens. They are treated with other therapies, yet their survival is not as good. Cardiac disease is also a major determinant of outcome and patients without cardiac disease do better than those with it. If you can get people through treatment and stop production of these deleterious light chains, patients can have a survival benefit.

Cardiac biomarkers have turned out to be very useful for prognosticating patients with amyloid cardiomyopathy. It is becoming accepted that staging can be accomplished independent of ECHO and clinical findings by looking at troponin and BNP levels. If both biomarkers are normal, then patients do well. If one or both are elevated, the chance of survival worsens. Our patient had a mildly elevated BNP, pretty normal troponin performance status, and minimal heart failure and was able to go through stem-cell mobilization. This was complicated by worsening pedal edema and slow ventricular tachycardia, which he tolerated but put him in the hospital for the rest of his therapy. He received high-dose intravenous melphalan and had no further complications. He was discharged soon after and continued as an outpatient awaiting neutrophil engraftment, which occurs with peripheral blood stem cells ten days later. He did well and had no neutropenic fever, no further hospitalizations, and a wonderful response over the years since that time. All of his hematologic parameters—including the bone marrow, paraproteins, and light chain levels—have normalized. The light chains quickly came down after high-dose chemotherapy. The cardiac biomarkers and ECHO measures also improved and a year later his BNP was down to 90 from 160. His septal thickness has gotten better by a couple of millimeters since treatment and there was no need to look at his ECHO.

In patients who present with very advanced heart disease when they are diagnosed can be a very different experience. Amyloidosis patients (n=26) were evaluated by Dey and colleagues. Patients with multi-organ disease and potential problems getting through the heart surgery were excluded, which left 18—9 died waiting for a transplant and 9 completed their transplant. Of the 9 transplanted patients, 8 had subsequent autologous stem-cell transplant, 6 of the 9 were in complete recovery, and only 5 of the 9 were alive at the time of this report. There really is no big difference between survival of patients with AL-amyloidosis and extensive cardiac amyloidosis. One of the issues with this disease is if you don’t kill the plasma cells and get rid of the light chains within 6-12 months, they recur in the transplant heart and patients will redevelop cardiac amyloidosis, which is a fatal process.

In summary, amyloidosis is an unusual and under-diagnosed disorder. Step one is to diagnose—suspicion in multisystem diseases or in cardiac disease with low-voltage electrocardiogram, thickened echocardiogram, diastolic dysfunction, and perhaps biopsy an involved organ or the fat pad. Once the diagnosis is made, type it to decide the best form of treatment, and then treat. Management of the disease is fairly different from management of heart failure. There
are ongoing studies in animal models, model imaging approaches, and therapies for these diseases that will eventually benefit our patients.

References


Hypertension and Cardiac Issues From the Perspective of the Practitioner

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“...about a third of oncology patients taking oral chemotherapy do not use their oral chemotherapy appropriately. The literature discusses non-adherence and compliance issues in general, yet you would think maybe people would take chemotherapy like they are supposed to because it is a high-stakes drug. The truth is that there are still lots of dilemmas and with the explosion of oral chemotherapeutic agents, oncology practices have not adjusted to the resources it takes to educate, monitor, and work through these problems.”

—Michael J. Fisch, MD, MPH, FACP

There is a lot of emphasis these days on quality care—quality referring to the degree to which our health services are consistent with current professional knowledge, increase the likelihood of desired outcomes, and provide coordination and continuity of care throughout the entire cancer
experience. When you look at that construct of quality, you can understand where the cardiac issues are vulnerable right now because the current professional knowledge is new and has not hit the textbooks. It certainly has not hit medical oncology board exams. The outcomes associated with what we consider better care, with respect to cardio-oncology issues, are not well understood yet. Data are still evolving and the coordination of continuity of care is a major challenge. For example, most oncologists pay attention to the cancer and the cancer treatment issues, but incorporating all important issues and enhancing the quality of care within the frame of reference (i.e., the patient with cancer) is a much larger task.

Through an email network (also know as the “regional center tumor board”) a variety of oncologists from different types of settings ask each other questions and deal with issues. The following scenario was emailed to the “regional center tumor board” for comment. A 49-year-old man with recurrent rectal cancer, some alcohol use, and lung metastases, was treated with FOLFOX-bevacizumab. His other diagnoses include obesity, diabetes, and hypertension (BP 160/92 with previous vitals in a similar range). The question to my colleagues being: Do you treat the hypertension? If so, what antihypertensives do you use? What are your goals? When you’re treating, what are you trying to achieve? How do you know you’ve been successful? How do you know what you’re titrating to? And then, if the blood pressure isn’t right, do you continue the bevacizumab? How do you know when to give it or not give it? Answer A: “I would treat the hypertension and continue with bevacizumab. I’ve used ACE inhibitors with some success and in my reading a few years ago, the standard meds, beta-blockers and ACE inhibitors, are considered reasonable. In a diabetic, an ACE inhibitor might be good. I’d target 120/80.” Decent answer. Answer B: “I’d offer bevacizumab and probably not treat the hypertension if the diastolic blood pressure is staying in the low 90s range. The Micromedex® page on dose modifications for bevacizumab indicates to adjust if the patient is in a hypertensive crisis or has hypertensive encephalopathy. I’ve gotten in the habit of referring patients to General Medicine for initiation of antihypertensive therapy or other significant changes in management.” From these responses it can be determined that some oncologists are owning and dealing with the problem (e.g., hypertension) and some are referring to others. There are many issues like this and sometimes the oncologists are worried about the follow-up frequency if they start antihypertensives, especially once their patients finish therapy—their clinic will keep getting the refill calls, so referring to another service is the preference. Now if you want to the general family physician involved, then think about their practice. Family physicians have a lot of patients and getting them involved on a quick basis, getting them to clinic when you need, and dealing with a complex patient, is not always welcome nor easy to do. It could be a little wishful thinking here to get the other doctors involved on a timely basis. From the email experiment, we observed that most, but not all, would treat hypertension and some would defer. Some had more aggressive goals than others with blood pressure care, no one suggested a beta-blocker, and no one could reference a standard. The best resource that nobody read was the article by Maitland and colleagues about assessment, surveillance, and management of blood pressure in patients.
receiving growth factor signal pathway inhibitors. None of my colleagues knew about that article.

How do you influence oncology care? ASCO is the professional organization that these oncologists belong to, they read the *Journal of Clinical Oncology*, and attend the ASCO meetings. They do not read the JNCI. The medical oncology board review had nothing about any of what we have talked about these past two days. In terms of the oncology board, there are no board review questions on any of this. Investigational protocols are not appreciated for how influential and trusted they are, yet when a physician is looking for information on how you are supposed to manage the hypertension, or whether to continue the bevacizumab, a protocol might be consulted because whoever built that protocol had it very carefully vetted. That’s as good a standard as I can find, and I can find it in real time. In order to interpret the information, when you get to the dose modifications it will say what to do with hypertension, you will have to understand what grade 3 hypertension means using the CTCAE 4.0.

Overall challenges, vitals and basic cardiovascular data are lacking, oncologists influenced by attribution of the cardiac issues and care trajectory, difficult to integrate primary care physicians/consultants in a timely fashion, and mid-level providers and clinic staff with limited cardiac knowledge/skills. For example, oncologists do best at controlling pain when it appears the pain is due to the cancer or cancer treatment. An oncologist who is seeing a patient with pain from some other condition may have the skills and ability to assess and treat, but don’t always. They will frequently withhold their prescribing or their referrals if they are not directly attributed to the medical issues they are treating. It is difficult to integrate other specialists, including cardiologists, in the community. Oncologists believe they cannot get other physicians involved, so many of them feel trapped in their own skill set, with respect to some of these things, unless it is an over-the-top issue. The other group to educate and influence would be the oncology nursing society and professional organizations where the support staff in cancer care are really going to play a role for what happens.

It would be nice if we had real specific quality indicators. If a patient has an elevated blood pressure on initiation of doxorubicin, then what, because, why? We don’t have those in our hands and reinforced with education yet. Non-adherence and over-adherence of medication is an issue, particularly when the drug regimens are complex. There is complexity involved in transitioning care or coordinating care with other providers. Even when the oncologist can find a willing provider who is going to help them, the patients want the oncologist’s blessing for additions or changes to their medication regimen. If patients don’t hear the okay, they don’t take the drug. It can become quite cumbersome—it takes some teaching along the way. Other providers aren’t always motivated to get involved. The oncologists that are out there will be really focused on what they do well. We’re going to have to engage other providers, such as nurses, physician assistants, pharmacists, and others who extend to make things happen in these other realms. If you want to do research about this issue, there’s no committee within any of the cooperative groups that looks at these kinds of problems. It is wide open for research.
In conclusion, oncologists need to figure out how to treat targeted agents and cardiotoxicity, extend survival and decrease cardiac morbidity, ensure patient safety and effectiveness, alleviate the shortage of oncologists, and explore cardiology issues as a novel realm of “cancer control” research.

References

Is Preventing and Optimally Treating Heart Failure in Cancer Patients a Reasonable Goal?
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“Is preventing and optimally treating heart failure in cancer patients a reasonable goal? Asking this question is a little bit like asking, is the Pope Catholic or is Dolly Parton country? The answer, of course, is yes.”
—JoAnn A. Lindenfeld, MD

Heart failure in patients with cancer is likely to become more prevalent. We have an aging population—71% of all cancer deaths are in patients age 65 and older. (National Center for Health Statistics. Vital Statistics of the United States, 2002. Hyattsville, MD). Most of our studies have excluded these older patients and patients with comorbidities, yet as cancer therapies are expanded to the general population, we are going to see a larger number of toxicities in an older, more comorbid population. There is data that the incidence of breast cancer and heart failure increase with age.¹ We would expect that cancer and heart disease, including heart failure, occur more commonly together than separately, because the risk factors are very similar.

A study of 5 and 10-year prevalence rates of heart failure in women, 66-70 years of age, being treated for breast cancer was conducted.² There was a high 10-year incidence of heart failure in those who received adriamycin (approximately 50%), yet in the non-adriamycin group it was nearly 35%. In those who received no chemotherapy at all, about 27% over a 10-year period developed heart failure. In the general population, if we age this group and make them 76-80, we would have about a 10% prevalence of heart failure at most. Extrapolate that to the breast cancer survivors who received no chemotherapy and the incidence of heart failure is two-and-a-half-fold.
what we would expect in the general population.

It is really important to focus on heart failure because the mortality is greater than the mortality from some cancers. Heart disease, whether it is heart failure or coronary disease, decreases the survival from colon cancer and decreases the survival in breast cancer. There are a number of reports that show any substantial comorbidities are associated with mortality. This study from Scotland shows that if the survival of heart failure improves, then so does the survival of many of these cancers. The mortality from heart failure in both women and men is worse than the mortality from some cancers. It will be important for us to look at long-term survival.

The Early Breast Cancer Trialist Collaborative Group (EBCTCG), which has made a number of reports, did a meta-analysis of 40 randomized trials comparing surgery, or surgery plus radiation therapy, in women who had breast cancer, and were treated over a four-year period. What they found was that breast cancer deaths were reduced, but overall mortality was not reduced because there was an increase in cardiovascular disease. This took some time to appear, so as we look at heart failure and see the risks, we cannot rely on 2 and 3-year studies. We need to keep looking down the line and make sure that we haven’t adversely affected our mortality with heart failure. It is important to study patients who have cancer who appear to have a higher incidence of cardiovascular disease because it is not just the cancer chemotherapy. These patients have a higher prevalence of comorbidities from heart failure, so it is going to be important to recognize all of these issues.

As cardiologists, we worry about heart failure and treating it. Our oncology colleagues are very concerned about some of the therapies and recommendations that might limit, prevent, or prolong the time to effective cancer therapy. Once you develop heart failure, many anti-cancer therapies are contraindicated and there is LV systolic dysfunction along with a number of issues that complicate care. For example, multiple providers complicate care. One provider may recommend one thing, another recommend something else, and so on. The patient is confused and there are now polypharmacy issues added to the problem list. Symptoms of both heart failure and anti-cancer therapy may limit therapy and the patient’s tolerance for therapy. The social and financial issues from these two combined problems may limit therapy.

Researchers looked at the number of providers that the average Medicare patient with a diagnosis of heart failure, not cancer, sees in the average year. This would be complicated if the cancer diagnosis was added. The average Medicare patient with heart failure has 23 sites that provide care and 11 total providers that actually write prescriptions. This is very complicated care for the average heart failure patient. Now, what about the number of prescriptions? The total number of prescriptions per Medicare patient, without self-reported heart failure, is 29 per year. Those Medicare patients who have heart failure have 62 prescriptions written per year. This is an overwhelming complexity to care.

What complicates cancer therapy when you develop heart failure? Many drugs are indicated in the prolonged QTc (e.g., methadone, antiemetics, and antibiotics) and a patient with heart failure and
systolic dysfunction more often has a prolonged QTc than not. This is from patients admitted with acute heart failure—systolic dysfunction and heart failure with preserved ejection fraction—and they looked at prolonged QTc. Myocardial disease, prolonged QTc, is common in 66% of men and 75% of women—women have a more prolonged QTc because they are more susceptible. Once heart failure develops, go back and look at that QTc as it is very likely to be prolonged. This is true in outpatients with heart failure and systolic dysfunction also.

Characteristics common between aging, heart failure, and cancer might limit our therapy and add to the quality of life burden in these patients. Not only are comorbidities common in all three, but functional impairment is common in all three also. So, if the patient is totally fatigued, do we add a beta-blocker for heart failure? The patient is so fatigued they can barely get up in the morning, so do we limit chemotherapy? How do we put all of these together? Polypharmacy is common in all these. Anemia is common in all these. It is not just about symptoms. It’s social and financial issues that limit therapy in these patients. If you look at the older person with cancer and heart failure, they often have depression and cognitive impairment. They have inadequate care because they can’t get back and forth to the doctor easily or may not all drive due to limitations. A number of limitations, yet is this reasonable to address? Of course it’s reasonable because the ultimate goal is the total improvement on quality of life and survival in these patients, so we have to address these issues.

Is it possible? Yes, it is possible, yet we have a ways to go. Do we know how to treat heart failure in cancer patients? Can we be sure by doing this that we don’t prolong or limit anti-cancer therapy to also improve quality of life and survival from the cancer? How do we prevent heart failure in cancer patients? When we do studies to prevent cardiac toxicity or prevent heart failure, we need to select the riskiest groups. Do we need to do prevention in everyone? Do we need to add that burden to every single patient? Can we predict risk factors, heart failure by risk factors and/or biomarkers? We’ve seen some of that data and we can. Is it important to be selective there? Yes, it is because the more specific we can be, the better we’ll treat all the patients, because we can avoid treatment in some. How long should people take preventative therapy? Do we mask some cardiomyopathy? If we were to give everyone ACE inhibitors or beta-blockers would we mask some cardiac toxicity we haven’t seen? Do they need these medications long-term? How do we evaluate that?

Do we know how to treat heart failure in cancer patients? We have discussed heart failure here with drugs that cause systolic dysfunction. Half of all the people in the world have heart failure with preserved ejection fraction (EF). If we look at the frequency of preserved EF in hospitalized patients and outpatients (women and men) with congestive heart failure, about half have preserved systolic function with actual heart failure—more common in women than men. We have not focused on heart failure with preserved systolic function, yet I am starting to see some of these patients. A number of factors that provoke heart failure with preserved EF: hypertension, aging, atherosclerosis, and diabetes. You can see that hypertrophy, fibrosis, and endothelial dysfunction are all a component of this. Perhaps we should be looking at this as a cause of fatigue more than we have been. We know how to treat heart failure with systolic dysfunction in other arenas, and there is data in anti-
cancer therapy. These are the therapies that we know are definitely beneficial for survival and quality of life—ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists. Now we need to even go farther and know who to treat and who not to treat and how rapidly can we treat these patients.

Our normal course for heart failure therapy is to increase the beta-blockers every two weeks to a maximum dose of the beta-blocker. That’s a two-month period. Do we want to delay anti-cancer therapy? Can we do it faster in these patients? Can we get them back to chemotherapy? This is important for us to consider as cardiologists, because our oncology colleagues consider this all the time. Are the same therapies beneficial? If we do beta-blockers, do we need ACE inhibitors? Do we need to take the time to put in all the therapies that are guideline-created? We need to think about that. What is the most effective therapy, and how do we get that onboard fast, and then add the others as we get back to our anti-cancer therapy? Is the timeframe the same? Is the natural history the same? Do we know exactly the right drugs? Are all the drugs necessary or incrementally helpful? Do we have to add on all the drugs? These patients already have a big burden managing all these drugs. Are the drugs forever? If you receive a cardiotoxic chemotherapy, and your EF goes back to normal, do you need to continue it forever? Can we accelerate the initiation of therapy? We have to think about all these questions so that we do not limit or prolong our anti-cancer therapy any more than necessary. For the patient, we need to get these complex therapies together and create algorithms that are easy for the patients and the physicians to initiate and to consolidate and improve care.

So is it reasonable? Yes. Is it possible? Yes. We have to create a partnership that emphasizes not cancer survival and not heart failure survival, but all-cause survival and quality of life. The endpoint is all-cause survival and quality of life.

References
Closing Remarks

**Lenihan:** The top three priorities, all of equal value, regarding this conference were to:
1) enhance and participate actively in research so we understand what the best treatment is in these difficult situations; 2) ensure there is multidisciplinary input for any recommendation or educational program we have—we need to do a better job of getting nurses, nurse practitioners, and pharmacists engaged in the whole process; and 3) provide a summary document that guides us on how to detect and manage cardiotoxicities as they occur.

**Cipolla:** We live with these issues [cardiotoxicities in cancer chemotherapy patients] every day. We are [on the brink] of specialization on something very important—it is important to consider the patient as a whole, not just for their cancer pathology. Three priorities regarding this conference: 1) to change the culture—educate our colleagues to look at the overall consequences of what they are doing and encourage them to create a synergistic partnership between different knowledge bases; 2) to build a system of drug development that allows, in the very early stages, the testing to understand if there is a chance of cardiotoxicity or not—we have to help the pharmaceutical industry develop this new system; and 3) to build a collection of scientific and practical data for physicians to share information with one another.

**Lenihan:** Our whole purpose of the International CardiOncology Symposium and the Cardiology & Oncology Partnership is to get physicians [cardiologists and oncologists] to communicate and cooperate more effectively, provide more practical evidence for evaluating cardiotoxicity, and educate physicians to understand that protecting the cancer patient from heart failure can be interjected into the everyday workflow. The key piece is to embody effective communication about disciplines with the patient being the focus of what we are doing.

**Cipolla:** [The International CardiOncology Society] should be owned by anyone and everyone who wants to be inside. In my opinion, the scientists that are present here, are really interested in what we are doing together and I believe that this will only be much more important in the future.

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