International CardiOncology Society
Fifth Annual International Symposium

October 5–6, 2011
Silver Spring, Maryland
Selected Proceedings of the
Fifth Annual International Symposium
of the International CardiOncology Society
in conjunction with the
Cardiac Safety Research Consortium
and hosted by the Food and Drug Administration
Dear Colleagues:

It is our great pleasure to introduce you to the International CardiOncology Society which held its Fifth Annual Meeting hosted by the Food and Drug Administration in Silver Spring, Maryland, on October 5–6, 2011, in conjunction with the Cardiac Safety Research Consortium. The proceedings from this important international meeting are distilled here in a carefully prepared document which represents the most updated developments in the field of cardiac disease in cancer patients and highlights many areas of substantial clinical overlap between the disciplines of Cardiology and Oncology. This is a burgeoning area of medical care largely because of the success of cancer therapy and the direct interaction between therapeutic targets and the demographics of patients who are seen by providers in both disciplines.

This meeting had a combined representation of Cardiologists, Oncologists, and Primary Care Physicians who practice in governmental, industry, institutional and community-based practices and have extensive experience in the challenging clinical decisions when 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.

We are honored to present a summary of 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 (cardioncology.com).

Please enjoy and join our group of friends!

Sincerely,

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Overview of the American College of Cardiology Registries

Jack Lewin, MD
Chief Executive Officer, American College of Cardiology, Washington, DC

“*The goal is to advance science and accelerate our ability to provide quality care with better outcomes and promote innovation.*”

— Jack Lewin, MD

The American College of Cardiology (ACC) is an organization of 40,000 members—> 90% of the current United States cardiologists (virtually all the practicing cardiologists and researchers); 5,000 international fellows (FACC); 5,000 advanced practice nurses and a significant number of cardiovascular pharmacists, and, of course, many fellows and clinicians in training. The ACC has become a global organization.

For over a decade the ACC, with The Society for Thoracic Surgeons, has been researching the building of registries to monitor outcomes related to the American Heart Association (AHA) guidelines and performance measures; appropriate economic and clinical use criteria built into these tools; the extent to which these tools are being used; and whether or not evidence-based medicine and the best science is really being practiced.

There has been a spotlight on the Food and Drug Administration (FDA) recently because it is time to get the Medical Device User Fee and Modernization Act and Prescription Drug User Fee Act reauthorized to ensure funding for this agency. The ACC is working on this because it is an important issue as well as critical for the college. In addition, the controversial issues surrounding rosiglitazone, rivaroxaban, and other applications for pending cardiovascular drugs has also placed the FDA in the spotlight. In regards to devices, there has been a risk tolerance and questions regarding how tightly we should focus on patient safety and still be innovative—the processes for approval have been under a lot of scrutiny. Device investors and venture capitalists seem to be moving offshore because they believe they can move faster with what they consider to be equal safety in the European Union and elsewhere—this is not in the United States’ best interest.

The FDA has a tough job in trying to balance innovation and moving drugs and devices to market quickly. Much of the criticism heaped on the FDA by society is because there is a fundamental lack of understanding regarding these processes. The FDA has to be cautious as it is under significant political scrutiny while the media, society, and a variety of American constituencies are demanding a zero tolerance policy in regards to patient safety—this is an extreme point of view as one cannot be innovative or develop new products in this type of environment.

There is a tremendous need for public education that must accompany this fight. For example, a very one-sided *Wall Street Journal* editorial pointed out how long it has taken to get aortic valve replacements in the US.¹ The technology has been developed here and when it is approved, we will be the forty-third country to apply it. Meanwhile, many people with no other option have
died while waiting for this. This is the situation.

By working with the FDA we can address these big political problems in a more effective manner. For example, the ACC registries are an excellent tool for post-market surveillance. The transcatheter aortic valve replacement and post-market surveillance registry is a project that the ACC has been working on in partnership with the FDA and the Centers for Medicare & Medicaid Services (CMS), the two regulatory agencies involved with getting this new technology to American patients who will benefit from it. There are some unprecedented, yet positive things happening in this arena.

The National Cardiovascular Data Registries (NCDR) is a partnership of many societies today—emergency physicians, neurologists, neurosurgeons, the AHA, and countless other cardiovascular societies who are partners in the registries with the ACC in various ways. The CathPCI Registry® was started in 1998 and now has 17 million patient records which includes 70% of the angioplasty and stent data in the US. This registry has become an absolute wealth of information in data, research, and clinical improvement opportunities.

The ICD Registry™ came next and the Centers for Medicare and Medicaid Services required the use of this registry for defibrillator placement or they would not reimburse hospitals—this became a very popular registry. In fact, the ICD Registry™ has 100% of the United States defibrillator placement data. A partnership with the federal government funded this and hospitals pay a nominal fee for the data collected—$3,000-4,000 per year per hospital—yet it allows the development of these registries to move forward.

The CARE Registry® is a small, yet important, registry for carotid artery stenting and endarterectomy procedures. The ACTION Registry® for acute coronary syndromes and heart attack evidence-based treatment is growing rapidly. Not all patients come in and get an angioplasty or stent, so this is an important registry. IMPACT Registry™ is for patients with congenital heart disease and the FDA are partners in funding the initiation of this registry.

An important new outpatient registry is the PINNACLE Registry™. Combine this registry with the NCDR inpatient suite and we can now follow patients over the continuum. The PINNACLE Registry™ is the first office-based quality improvement program in the US that serves as a dashboard of clinical decision support and continuous feedback on about thirty different measures. It also has some operational management tools and is compatible with more than 24 electronic health record (EHR) systems. This allows us, via data extraction system integrator technology, to go into the EHR, pull the data out, harmonize the standards between the 24 EHRs, and give physicians feedback without having them enter new data at the point of care. Recently I learned there is a whole contingent of PINNACLE Registry™ users in India who have started reporting to the US. The registry now includes Medicare, private insurers, and others—this is a big deal.

Limitations are few, yet they exist. We want this registry to be populated with people who are most like our patients, so the concern is we need the very elderly, who are oftentimes the people with the most serious cardiovascular situations; pediatric patients; and diversity in regards to ethnicities and gender. The goal is to advance science and accelerate our ability to provide quality care with
better outcomes and promote innovation. So how can we best utilize these registries?

Approximately 23% of patients who had an ICD implanted did not have the device implanted according to the accepted guidelines. In all fairness, the guidelines needed to be updated as there is new science to add, so the real number may be 10-15%. Similarly, we know that 11% of stents for chronic stable angina should not have been placed and a significant number of cardiac catheterizations and angiographies did not need to be applied to patients—the nationwide disparities are great. The point being that there is a great deal of variation that can be addressed with the registry data. The hospitals are being given this data and have to sort out how to use it more appropriately. There are tremendous opportunities for reducing unnecessary admissions, readmissions, and complications.

These registries assist in measuring clinical effectiveness—applying the guidelines to performance indicators to actually measure performance, using that to measure outcomes, and then back to new concepts and clinical trials, that whole cycle of continuous improvement in outcomes and qualities. These registries are about consistently improving outcomes in efficient ways to improve and lower healthcare costs.

Science tells us what we can do, guidelines tell us what we should do, and registries tell us what we are actually doing. We are entering a time when real-world registry data and huge denominators of patients could actually be used in randomized control trials. Future technology will allow us to take real-world data, apply it through algorithms to get the equivalent of randomized control trials, and move more quickly and less expensively along the whole array of scientific questions that we need the resources to answer. Even with the billion-plus dollars from comparative effectiveness research, more is needed to answer the outstanding questions across medicine. By working together we can promote innovation while providing access to new devices faster and safer at the same time.

References

Late Cardiotoxicity or Just Poorly Recognized Cardiac Injury?
Daniela Cardinale, MD, PhD
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“If we predict cardiotoxicity very early using biomarkers, particularly troponin, we can avoid it. If we wait for onset of symptoms, then we have to consider cardiotoxicity to be a truly irreversible disease.”
—Daniela Cardinale, MD, PhD

Cardiotoxicity is one of the major adverse effects of anthracycline (AC) administration and
is traditionally classified into different forms (i.e., acute and chronic) according to the timing of symptoms occurrence and its clinical course. The acute form occurs during or within two weeks after AC administration, yet not frequently, and is usually reversible with a good prognosis when it does occur.\textsuperscript{1,2}

Chronic cardiotoxicity has two forms—early onset cardiotoxicity, when symptoms occur within one year post-AC treatment, and late onset cardiotoxicity, when symptoms occur after one year.\textsuperscript{1,2} The typical clinical manifestation of chronic cardiotoxicity is a dilated-hypokinetic cardiomyopathy, usually irreversible, and traditionally considered to be refractory to the standard heart failure therapy and has a poor prognosis. Available data from the literature report that this form of cardiomyopathy has an especially poor prognosis when compared with other, more frequent forms such as ischemic or primary cardiomyopathy, with a two-year mortality rate of about 60%.\textsuperscript{3} This form of cardiomyopathy is believed to be refractory to conventional heart failure therapy, yet this opinion is based on anecdotal data coming from small, retrospective studies, in which standard heart failure therapy included only digoxin and diuretics. Moreover, this classification is made on retrospective studies reporting a late onset of heart failure symptoms. In studies with post-chemotherapy childhood cancer survivor populations, patients referred to the cardiologist only when heart failure symptoms occurred and cardiac dysfunction was confirmed by echocardiogram or nuclear angiography.\textsuperscript{4,5} The incidence of cardiotoxicity, of cardiac dysfunction, increased in parallel with the time elapsed from the conclusion of chemotherapy.

So getting back to our cardiomyopathy classification, we understand that there are many limitations because it is based on data obtained only from retrospective studies and mainly from childhood cancer survivors. In addition, no studies have evaluated the incidence of chronic cardiotoxicity in populations prospectively monitored for more than one year. The diagnosis of cardiotoxicity was always based on symptoms, or on occasional left ventricular ejection fraction (LVEF) evaluation for cancer relapse, and there is a lack of prospective evaluations of response to modern heart failure therapy.\textsuperscript{6-16}

In my opinion, the major questions we have to address are—Is cardiotoxicity really irreversible? Does late onset cardiotoxicity really exist? Or are we talking about a late diagnosis rather than a late onset disease? So let us try to answer these questions.

We recently evaluated the response to modern heart failure therapy, including angiotensin converting enzyme (ACE) inhibitors and beta-blockers in 201 patients with asymptomatic or symptomatic AC-induced cardiomyopathy.\textsuperscript{17} The major finding of our study is that the time factor is crucial. We found that early treatment—defined as within six months from the conclusion of chemotherapy—with an association of ACE inhibitors and beta blockers, allowed for a complete recovery of cardiac function in 42% of patients, and for a positive cardiac outcome. We also found there was a strong relationship between the time elapsed from the conclusion of chemotherapy/beginning of heart failure therapy and the LVEF increase in response to heart failure therapy during the follow-up. The more time passes, the less recovery possibility. In our study, the percentage
of patients who completely recovered from cardiac dysfunction, called responders, progressively
decreased as the time elapsed from the conclusion of chemotherapy increased. There was partial
recovery after six months, and the possibility to obtain at least a partial recovery was completely
exhausted after 12 months.

These results emphasize the crucial importance of an aggressive, prompt and early approach
in order to treat this kind of cardiomyopathy. So the answer to the first question: it would appear
that cardiotoxicity due to ACs is irreversible. Our data suggests that an early treatment, with a
combination of ACE inhibitors and beta blockers, allows for a complete recovery.

In order to try to answer the next questions, we designed a prospective study, including
patients treated with AC, in which we regularly, prospectively monitored cardiac function with
echocardiogram. The 3,000-patient study measured the occurrence of classically defined cardiotocicity. If cardiototoxicity occurred, a treatment with ACE inhibitors and beta blockers was initiated
and titrated to the maximum tolerated dose.

The preliminary data for the first 1400 patients, mainly women, evaluated to date is as
follows. The mean age was 50 years; mean baseline value of LVEF was 63%; mean AC cumulative
dose was 253 mg/m²; and the mean duration of follow up was six years, ranging from one
month to 17 years. In our study, 148 patients (11% of the study population) developed cardiotoxicity. Patients developing cardiotoxicity were older, more often males, and received a higher cumulative
dose of AC. No significant differences in terms of other cardiovascular risk factors or mediastinum radiotherapy were observed. The mean duration of follow-up was similar in both subgroups.

A multivariable analysis adjusted for gender, age, other cardiovascular risk factors, cumulative
dose, mediastinum radiation therapy and length of follow up and cumulative dose, male gender,
and age were selected as independent predictors of cardiotoxicity. However, only cumulative dose
and age were confirmed as predictors by cross-validation analysis. The diagnosis of cardiotoxicity
was made at the scheduled echocardiogram controls. In 13 patients, referring symptoms of heart
failure—mainly a reduction in left ventricular ejection fraction threshold—caused an adjunctive
echocardiogram to be performed to confirm the presence of cardiac dysfunction.

All cases of cardiotoxicity occurred within 18 months. No cases occurred after this time.
The cumulative percentage of cardiotoxicity was 57% at three months and 91% at six months.
By regularly monitoring these patients for six months, we were able to detect 91% of all cases
of cardiotoxicity. We treated patients developing cardiotoxicity with a combination of an ACE
inhibitor and a beta-blocker in 80% of cases. In 20% of cases, we treated patients with an ACE
inhibitor or a beta-blocker. In 146 patients (99%), the final LVEF value was higher than 50%; two
patients did not reach the value of 50% but an increase in LVEF of at least ten absolute points was
observed. The meantime of LVEF normalization was five months. But notably, the final mean
value of LVEF was significantly lower than the baseline value.

Our preliminary data suggests that only one kind of chronic cardiotoxicity seems to exist.
Monitoring cardiac function the first two years post-chemotherapy allows for the early detection
of cardiotoxicity in most patients who are still in the asymptomatic phase and for the treatment of cardiotoxicity in a reversible phase when partial or complete recovery is still possible. We can diagnose cardiotoxicity using different approaches from the evidence of heart failure symptoms occurrence, yet they can occur late, many years after the end of chemotherapy (e.g., 20 years or more according to the literature), so the range of time for diagnosis is very long. We can diagnose cardiotoxicity by regularly monitoring LVEF by echocardiogram and our data suggests that we can detect all cases within 18 months. Today, we also have the ability to detect cardiotoxicity at a preclinical phase, long before any changes in LVEF, using biomarkers—troponins in particular.

In previous studies, we observed an increase in troponin I shortly after chemotherapy.\textsuperscript{18} This increase predicted the development of cardiac dysfunction (i.e., a LVEF drop) during the following months, as well as its severity. In fact, we found a strong relationship between the maximum value of troponin I soon after chemotherapy and the degree of the severity of LVEF drop observed during the follow-up. We also demonstrated that an early treatment with enalapril in patients showing an increase in the marker, during or soon after chemotherapy, and continued for one year, prevents cardiac dysfunction and associated cardiac events.\textsuperscript{19}

We apply this approach to our daily clinical practice. We measure troponin I immediately before and after each cycle of chemotherapy. In patients showing an increase in troponin, we promptly start treatment with enalapril and continue this treatment for one year. We have treated and monitored more than 1350 patients in this way. We have not observed a significant reduction in cardiac function involving patients showing an increase in the biomarker and those patients not showing an increase in the marker after at least two years.

In conclusion, cardiotoxicity is a continuous phenomenon, starting from myocardial cell injury, followed by left ventricular dysfunction and then heart failure. We can detect cardiotoxicity in all of these phases, depending on the diagnostic tool used. The possibility of treatment changes accordingly if we diagnose cardiotoxicity early during cancer treatment with biomarkers, we can avoid it; if we detect cardiotoxicity, monitoring regularly cardiac function by echocardiogram, we have a high possibility of complete or partial reversibility; yet if we wait for symptoms to onset, we have to consider cardiotoxicity as a truly irreversible disease.

References


How Can Cardiology Help in the Development and Conduct of a Clinical Trial for Oncology?

Thomas M. Suter, MD
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“‘I believe there is a role for cardiologists to assist oncologists in deciding...how can we improve the reporting and how can we improve the measurement.’

— Thomas M. Suter, MD

It is important to understand our role as cardiologists in oncology based on the clinical trials that, by and large, are breast cancer trials with new compounds in which most of these patients have been pretreated with anthracyclines. One of the important points to always remember is that ultimately these patients need treatment. In 2001, someone at a heart failure meeting said, “Rituximab is cardiotoxic. Why don’t you guys just stop using it?” This is not the way to go. As cardiologists we need to support our friends in oncology so that they can use these drugs and by doing so, we should conduct large clinical trials where we try to detect, record, analyze, and report whatever we find.

Cardiotoxicity or cardiovascular side effects in oncology includes arrhythmias, cardiac dysfunction, thromboembolism, ischemia, and hypertension. For the purpose of the clinical trials in which I am involved, the issues are arrhythmias, cardiac dysfunction, and hypertension. Now QT arrhythmias is actually not a major issue anymore. Many of these drugs don’t really cause QT prolongation and, if they do, we now have methods (e.g., automated electrocardiogram machines) which negate this as a major issue.

The larger issue is actually hypertension. Hypertension is occurring with some of these newer drugs we are using in clinical trials. Whether or not these drugs make it to market remains to be seen. In addition, and this may seem very basic, you cannot expect a regular oncology nurse to actually know how to use a blood pressure cuff. So one of our first steps is to teach the nurses how to take an accurate blood pressure—use the right size cuff, initially measure both arms, let the patient sit down for ten or fifteen minutes before you even record your blood pressure, and so forth. If we don’t get the baseline data right, we will never be able to figure out what is happening with the patient. We have travelled all around the world to teach people how to do this.

Then comes the report. This is something I still struggle with and I hope to get some guidance from ICOS. My dilemma is when and how do we report our findings? What classifications do we use? Do we use JNC 7, JNC 8 or the European classification? Or do we continue what we normally do and use the common terminology criteria for adverse events in cancer patients? The problem with that is lack of specificity—there are ranges of hypertension. The newer versions of the Common Terminology Criteria for Adverse Events (CTCAE) are better, yet we still struggle with when and how we report. For example, what do we call a hypertensive event? Do we call a
hypertensive event if it only happened once? Do we call a hypertensive event if the patient experienced long-term hypertension? What is hypertension overall? We are struggling with all of these classifications; therefore I believe that one of the roles we have as cardiologists, and as the ICOS, is to come up with a common set of acceptable definitions for hypertension and its classifications.

Cardiac dysfunction heart failure—what exactly is heart failure (HF)? Tables 1 and 2 show the symptoms, history, and physical findings of HF.1 Being a trained heart failure guy, if we know

| Table 1. Use of the Medical History to Assess the Heart Failure Patient |

**Symptoms Associated With Heart Failure**
- Fatigue
- Shortness of breath at rest or during exercise
- Dyspnea
- Tachypnea
- Cough
- Diminished exercise capacity
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Nocturia
- Weight gain or weight loss
- Edema (of the extremities, scrotum, or elsewhere)
- Increasing abdominal girth or bloating
- Abdominal pain (particularly confined to the right upper quadrant)
- Loss of appetite or early satiety
- History of Cheyne-Stokes respirations during sleep (often reported by the family rather than by the patient)
- Somnolence or diminished mental acuity

**Historical Information Helpful in Determining if Symptoms Are Due to Heart Failure**
- A past history of heart failure
- Cardiac disease (e.g. coronary artery, valvular, or congenital disease; previous myocardial infarction)
- Risk factors for heart failure (e.g. diabetes, hypertension, obesity)
- Systemic illnesses that can involve the heart (e.g. amyloidosis, sarcoidosis, inherited neuromuscular diseases)
- Recent viral illness or history of human immunodeficiency virus infection or Chagas disease
- Family history of heart failure or sudden cardiac death
- Environmental or medical exposure to cardiotoxic substances
- Substance abuse
- Noncardiac illnesses that could affect the heart indirectly (including high-output states such as anemia, hyperthyroidism, arteriovenous fistulas)
what HF is, and I believe we do, then how do we teach our friends in oncology? How do we teach the oncology nurse how to detect heart failure? This is one of our biggest struggles. For example, we want to know whether or not a patient is capable of climbing one flight of stairs and if they are not, then we call them a class three patient. However, if we report this, do we report it according to the ACC/AHA new classification? If so, then all of our patients are class A; or do we classify it according to the New York Heart Association (NYHA) class; or, again, do we use the CTCAE criteria? Our classification system is better than it was in the past, yet it is still difficult to use. For example, we have left ventricular systolic dysfunction measured by a drop in ejection fraction as a class three event defined as symptomatic due to a drug. So what does that mean? Is this now heart failure? We have a class heart failure and I was taught that heart failure is when you have symptoms and the clinical findings together. So is this really heart failure? My point is that we have made progress with the classification, yet we need more progress. We need a unified classification system in this cardio-oncology environment.

Then we have inherent problems with how we measure. For example, our preference is to use echocardiography, yet this has an inherent problem in that inter- and intra-observer variability is

### Table 2. Physical Findings of Heart Failure

<table>
<thead>
<tr>
<th><strong>Tachycardia</strong></th>
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<tbody>
<tr>
<td>Extra beats or irregular rhythm</td>
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<tr>
<td>Narrow pulse pressure or thready pulse*</td>
</tr>
<tr>
<td>Pulsus alternans*</td>
</tr>
<tr>
<td><strong>Tachypnea</strong></td>
</tr>
<tr>
<td>Cool or mottled extremities*</td>
</tr>
<tr>
<td>Elevated jugular venous pressure</td>
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<tr>
<td>Dullness and diminished breath sounds at one or both lung bases</td>
</tr>
<tr>
<td>Rales, rhonchi, or wheezes</td>
</tr>
<tr>
<td>Apical impulse displaced leftward or inferiorly</td>
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<tr>
<td>Sustained apical impulse</td>
</tr>
<tr>
<td><strong>Parasternal lift</strong></td>
</tr>
<tr>
<td><em>S</em>₂ or <em>S</em>₄ (either palpable or audible)</td>
</tr>
<tr>
<td>Tricuspid or mitral regurgitant murmur</td>
</tr>
<tr>
<td>Hepatomegaly (often accompanied by right upper quadrant discomfort)</td>
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<tr>
<td><strong>Ascites</strong></td>
</tr>
<tr>
<td><strong>Presacral edema</strong></td>
</tr>
<tr>
<td>Anasarca*</td>
</tr>
<tr>
<td><strong>Pedal edema</strong></td>
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<tr>
<td>Chronic venous stasis changes</td>
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* Indicative of more severe disease.
quite significant—5-10%. So how do you account for that? We try to have centralized reviews of the echocardiogram for some of these trials. The problem now is cost and time because you need the echocardiogram to make a decision at the point of care. The echocardiogram will determine if the cancer treatment is continued or not. Again, I believe there is a role for cardiologists to assist oncologists in deciding how to deal with these changes, how can we improve the reporting, and how can we improve the measurement.

We also need to apply certain rules. For example, what do you do when the left ventricular ejection fraction (LVEF) drops? In most of these trials, we requested two measurements so if the LVEF dropped by more than 10% below 50% we waited and repeated the measurement again after three weeks. The big difference here is that the event rate drops dramatically because you are using two data points (i.e., two drops) to define one event, instead of two. The question here is, what is the real drop? Is the real drop when we see it once? Is the real drop when we see it repeated after three weeks? I think this is an area where further investigation is needed.

We also need to develop criteria as to what to do. For example, in many of these trials, we let the LVEF drop to below 40% before do anything. For example, we have continued trastuzumab, even if the LVEF dropped to below 50%, and responded when it dropped below 40%. The big question is what should we expect? That these new drugs cause cardiac dysfunction? We need to know what to expect and understand it, so we will know what to do next.

We also need to know what we are looking at in regards to the type of cardiotoxicity. Are we looking at chronic cardiotoxicity, or are we looking at a temporary, reversible event? For example, during the HERA trial, a patient dropped her LVEF, recovered, and then dropped again. Clearly the trend was decreasing over time and I would define this as chronic cardiotoxicity. In the same trial, we had another patient that dropped her LVEF to 40%, recovered, and then was fine. So we not only count drops in LVEF, we need to consider what happens to these patients over time? Patients survive because of these cancer drugs. We should always consider this and put the cardiology and oncology pieces into perspective.

There is a long list of what we should do. We should have surrogate markers, cardiac biomarkers, and new imaging. We need long-term follow up and treatment trials. The limitation here is actually money. Perhaps this is something the ICOS can work on—real time trials. The important thing is that we look at long-term cardiotoxicity. For example, the HERA trial treatment was 48 months and there was not much ongoing. If we followed patients up to 10 years, then the outcome might be different. My wish list for this oncology trial is further collaboration—useful clinical endpoints and common definitions need to be developed. It would be nearly impossible to conduct all of these trials for up to ten years, so we need good surrogate markers to predict what is going to happen with these patients, in addition to long-term follow up and treatment trials.

In conclusion, by using standard procedures and checklists, pilots have taken a relatively dangerous endeavor of flying to a level which is now quite safe. This is one of the things we should envision also as potentially cardiotoxic compounds are placed on the market. We must
develop standard procedures and protocols, and then I believe we can have a big impact on cardiology clinical trials.

References

New Developments in Echocardiographic Detection of Cardiotoxicity
Carol L. Chen, MD
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“Strain has revealed early and sustained abnormal myocardial contractility in the setting of normal LVEF, during and after treatment with radiation, anthracycline, and/or trastuzumab therapy. However, it’s still unclear what this means clinically.”
—Carol L. Chen, MD

It is clear that detection of cardiotoxicity by left ventricular ejection fraction (LVEF) measurement is too late. Two-dimensional LVEF is inadequate because it’s a measurement of volume change, not a direct measurement of contractility, and is subject to loading conditions. It is well documented that we have a 5–10% intra- and inter-observer variability, which makes following LVEF difficult. The visual estimate is also often affected by a translational motion. So what else do we have?

Recently there’s been a lot of attention given to myocardial strain. Myocardial strain is a dimensionless index of myocardial contractility. It’s measured as a percentage of deformation from diastole to end-systole. The strained rate is the speed at which this deformation occurs. Strain has been considered in other cardiac diseases, such as coronary disease, hypertension, diabetes, heart failure, and non-obstructive hypertrophic cardiomyopathy, to demonstrate abnormal myocardial contractility and settings of normal LVEF. Tissue Doppler strain was originally being used, however it’s been surpassed by 2D speckle tracking. Tissue Doppler strain is the measurement of myocardial tissue velocity parallel to the ultrasound beam in relationship to the ultrasound transducer, and is subject to noise and angle dependence. 2D speckle strain is angle independent and less subject to noise. In speckle strain tracking, the myocardium’s natural acoustic characters which allow for software to track the myocardium in multiple dimensions—in longitudinal, radial, and circumferential deformation—giving us multiple axes for looking at myocardial contractility.

There have been studies observing the use of strain in detecting cardiac effects in cancer treatment. A European study researched breast radiation and effects on the myocardium using strain.
Investigators looked at 30 patients, 20 patients with left-sided disease and 10 patients with right-sided disease, and correlated it with the degree of radiation exposure. Left-sided breast radiation exposes more myocardium to radiation effects compared with right-sided radiation. In looking at conventional echocardiogram parameters, LVEF remained within normal limits, pre-radiation therapy (RT), post-RT, and during the two-month follow up (Figure 1). There was a small decrease in LVEF after RT in left-sided radiation patients, yet when the patients who were exposed to anthracyclines (AC) were removed from the group, this became insignificant. When studying regional differences in longitudinal strain and strain rate, investigators found the function of the apical regions were much more affected than the mid or basal segments with RT on the left side. The degree of radiation exposure in these patients correlated with the degree of abnormal strain, yet there was no long-term follow-up or clinical outcomes. This does remind us that with left-sided breast radiation there is some cardiac effect yet long-term significance remains unknown.

The same investigators also looked at the cardiac effects of pegylated liposomal doxorubicin in a small group of elderly patients. Pegylated doxorubicin has a safe cardiac profile. They performed Doppler strain and strain rate imaging over six cycles of pegylated doxorubicin and they found that although LVEF remained completely normal throughout treatment, longitudinal strain and radial strain declined in these patients compared to their baseline. Radial strain measurements declined first, followed by longitudinal strain, after six cycles. Again, there was no long-term follow up, yet it does remind us that liposomal doxorubicin has a cardiac effect although we don’t know what it means clinically.

Hare and colleagues studied a selection of 35 breast cancer patients receiving trastuzumab therapy. Over 90% had already been exposed to doxorubicin and cyclophosphamide. These
patients were followed over 12 months, with serial echocardiograms assessing at 2D LVEF, 3D LVEF, and a large number of strain parameters and diastolic indices. They found that all LVEF—whether 2D or 3D—remained above 50% and were not changed as a group throughout the 12 months. However, there was a decline in 2D longitudinal strain rate and 2D radial strain rate. In 25% of patients, there was a decline of about 10% LVEF; a significant decline in 2D longitudinal strain in over 50% of these patients; and about 30–40% of these patients also had a decline in the radial strain. Of the 18 patients who had a decline in their strain rate, three of them had a concurrent decline in LVEF, and an additional two more went on to develop clinical LV dysfunction in the 20 months that followed.

Another study observed about 45 patients in a four center trial, undergoing AC/cyclophosphamide and trastuzumab therapy for breast cancer. The cardiotoxicity was defined (per the trastuzumab guidelines) as a LVEF decline to < 55% and decline of 5% without symptoms or 10% with symptoms. When dividing the patients this way, they found that a drop in LVEF was not predictive of cardiotoxicity, yet a decline in longitudinal strain was. When reviewing the analysis of cardiotoxicity predictors, an elevation of highly sensitive troponin I at three months was also predictive of cardiotoxicity at six months, as well as a longitudinal and radial strain at three months was also an independent predictor of cardiotoxicity at six months. Investigators also found a very high negative predictive value for looking at strain and the presence of elevated troponin at three months. This can be very helpful in a clinical setting, if it proves to be true.

Another small study looking at 42 patients had similar findings of decline in tissue Doppler and global and radial strain preceding LVEF decline in a segment of this population. Investigators also added MRI findings and found that there was a delayed enhancement in all ten patients who had a decline in LVEF, suggesting a scar. In this study, there was no change in troponin T, B-type natriuretic peptide (BNP), or C-reactive protein (CRP) during these six months.

Strain has also been looked at in terms of surveillance of survivors of these cardiotoxic therapies. In pediatric survivors of doxorubicin, Ganame and colleagues reported that 56 asymptomatic pediatric patients, who had survived a fairly low dose of AC therapy with normal LVEF, had reduced tissue Doppler, radial and longitudinal peak strain rate, and strain, compared with the healthy cohort. Cheung and colleagues recorded in 45 patients who had finished acute lymphoblastic leukemia treatment, with a mean dose of doxorubicin of only 240 mg/m², that they also had reduced global strain and circumferential strain rate compared with a healthy cohort. These investigators also used strain to look at dyssynchrony and found a higher prevalence in these patients than in control.

At Memorial Sloan-Kettering Cancer Center, we are looking at adult cancer survivors of AC therapy that was received as a child or young adult. We have analyzed 85 patients who have been long term survivors (15 years since their last treatment). Using longitudinal 2D global strain, we have been able to consistently analyze 18 segments. Of these patients, 14% had abnormal LVEF, even though they were asymptomatic as defined by an LVEF < 55%; however, 35% of these patients had an abnormal average global 2D longitudinal strain using a normative value
of < -18% as defined by Marwick.\textsuperscript{10}

In long-term survivors of Hodgkin’s lymphoma who were treated in the 1980s with high dose mediastinal radiation with or without AC therapy, investigators looked at global longitudinal strain in comparison to healthy individuals.\textsuperscript{11} Patients who had completed radiation therapy 20 years prior had a significant decrease in global longitudinal strain and if they also had completed AC therapy, then global strain was even more markedly abnormal.

Breast cancer survivors who had AC-based treatment with or without adjuvant trastuzumab therapy over the past six years were compared with a healthy cohort.\textsuperscript{12} Investigators found a normal LVEF. In the treatment group, the global longitudinal 2D strain was decreased—26% with their global strain below the lower limit of the healthy cohort. Radial strain was not found to be different between the groups.

Most of the studies reviewed here are small and the clinical significance of the decline in strain and strain rate in the long-term is absolutely unclear. The jury is still out on whether or not abnormal strain parameters can predict clinical outcomes. There are obviously many different ways to measure strain—strain rate, tissue Doppler strain, radial, circumferential, longitudinal strain, regional strain. In other studies, radial strain or circumferential strain did not show differences, yet longitudinal did, sometimes strain rate did, and global strain did not. This is all still very unclear as to which measurement would be most feasible. The strain software remains completely proprietary and unique to each company, so that there are different normative values for each program and most normative values are still not agreed upon universally. We don’t know what degree of abnormality is that is clinically significant—is it a slight decline or one with multiple standard deviations? Strain is still dependent on the 2D image, so you have the same problems with strain analysis if the 2D image is poor. If you are foreshortened in the apical view, then the strain calculation will be inaccurate. If there is poor endocardial border resolution (e.g., apex for breast cancer patients) you will not be able to measure strain globally and accurately. This doesn’t mean that we should just throw away strain. I believe we should start to experiment with strain in our own labs and increase our expertise in using it.

One of my patients who is a young man who finished treatment for lymphoma with only 180 mg/m\textsuperscript{2} of doxorubicin. From his baseline to post doxorubicin echocardiogram, his LVEF declined to the low 50s, high 40s and we started him on carvedilol therapy. After a year, he wanted to stop the carvedilol. His LVEF had returned to normal range, yet I wasn’t quite sure that it looked completely normal. Global 2D longitudinal strain was analyzed to be -16% which is in the borderline range. According to Marwick, -18% and greater is normal, -16% to -18% is borderline, and < -16% is abnormal. After discussing with the patient what strain could mean, we decided to continue the carvedilol for the time being and reevaluate at a future date.

Another patient on trastuzumab developed a cardiomyopathy and had symptoms of heart failure. Her LVEF dropped to 35% and her global strain at that time was -14.8%. We started her on carvedilol and an angiotensin converting enzyme (ACE) inhibitor and stopped trastuzumab.
On repeat, her echocardiogram looked a little bit better—about 50%—and we did another strain analysis and it improved to about -16.6%, which is in the borderline range. She continued on her carvedilol and ACE inhibitor and was allowed to be re-challenged with trastuzumab.

In summary, strain has revealed early and sustained abnormal myocardial contractility in the setting of normal LVEF, during and after treatment with radiation, AC, and/or trastuzumab therapy. However, it’s still unclear what this means clinically. 2D global longitudinal strain data is promising to identify higher risk groups who should have closer follow up and continue or start cardiac medications. However, larger populations with longer follow up is definitely necessary to make this technology clinically relevant.

References
Anti-angiogenic and Anti-VEGF Therapy: A Cardiologist’s Perspective of the Disturbed Balance Between Vascular Protection and Anti-angiogenesis

Bonnie Ky, MD, MSCE, FACC
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“The goal of biomarker use is] early detection of cardiotoxic effects so we can improve prediction and identify the high risk patients; initiate early cardio-protective strategies and prevent dose interruptions; tailor a cancer therapy regimen to help decrease the cardiac risk and increase vigilance with aggressive risk factor modification; and, improve our mechanistic understanding of the disease process.”

— Bonnie Ky, MD, MSCE, FACC

The vascular endothelial growth factor (VEGF) system has undoubtedly important effects in terms of production of nitric oxide, proliferation, cell survival, migration, and permeability. With critical functions, such as angiogenesis, the maintenance of endothelial cell integrity, vascular tone, and endothelial cell platelet homeostasis, it is entirely biologically plausible that you could have hypertension, thrombosis, and cardiac dysfunction with inhibitors (e.g., bevacizumab, sunitinib, sorafenib).

With sunitinib, axitinib, bevacizumab, for example, there’s been a large meta-analysis published, a number of phase two trials, and randomized studies that demonstrate a significant incidence (about 22%) of hypertension overall; worse in the renal cell carcinoma population (up to 26%); potentially worse with axitinib (45-58%) and somewhere in the intermediate range with bevacizumab (24-36%).1-6 A clinically significant risk of cardiac dysfunction also exists, so a meta-analysis was published looking at 16 phase II, III studies.7 Nearly 7000 patients, demonstrating all heart failure incidence risk of nearly four percent, equating to a relative risk of 1.8. In terms of the high grade relative risk, this was on the order of 3.3. Similarly, bevacizumab has also been demonstrated to have a real risk of heart failure.8

So what is the cardiologist’s view? In other words, what keeps me awake at night are important unanswered questions, including: What are the precise biologic mechanisms of cardiotoxicity secondary to anti-angiogenesis therapy? Can we identify the at-risk patient undergoing anti-VEGF therapy? How can we better manage the risk of cardiotoxicity before it occurs and once it occurs? What can we learn from heart failure? How can we translate that knowledge and data? Let’s address these questions one at a time.

First, what is the role of the VEGF system in cardiovascular disease and remodeling? The VEGF system is undoubtedly highly complex, with numerous ligands, including VEGF-A, B,
C, D, E, and F. There is also placental growth factor (PlFG) that binds in numerous receptors—VEGFR-1, 2, 3 and neuropilin-1 and 2. There are a number of clinical downstream mediators that are activated, included PI 3-kinase, protein kinase B (AKT), nitric oxide, and mitogen-activated protein (MAP) kinase that have diverse properties.

There are five major ligands, and numerous receptors expressed in tissues such as placenta, lung, thyroid, goiter, heart, skull to muscle and vascular muscle cells, with diverse biologic activities, including vascular digenesis, angiogenesis, maintenance of homeostasis, recruitment of bone marrow derived cells, and lymphangiogenesis (Table 1).9-11 What does the knockout mouse phenotype tell us? It ranges from the most severe with VEGF (e.g., embryonic lethality) to an intermediate phenotype (e.g., impaired neovascularization response to myocardial infarct) to the normal phenotype with VEGF-D.

How about the receptors? VEGFR-1 has been shown to have important angiogenic functions and is also known as the FMS-like tyrosine kinase receptor Flt-1, and serves as a receptor for PlGF, VEGF-A, and B.9,12-13 It is expressed in diverse cell types and has been out-regulated during angiogenesis and hypoxia. It also has non-angiogenic and anti-apoptotic effects and under hypoxic conditions and oxidative stress, there is increased cardiomyocytic expression of Flt-1 or VEGFR-1. VEGF-B delivery to cardiomyocytes activates genes in contractility, calcium handling, hypertrophy, and energetics. VEGF-B delivery to tachycardia-induced cardiomyopathy models demonstrates less fibrosis and improves contractility. Flt-1 also circulates as a soluble anti-

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Receptor</th>
<th>Source</th>
<th>Biologic Activities</th>
<th>KO Mouse Pheno.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF-A</td>
<td>VEGFR-1, VEGFR-2, NP-1, NP-2</td>
<td>Almost all vascularized tissues</td>
<td>Vasculogenesis, angiogenesis, homeostasis, permeability, bone marrow derived cells</td>
<td>Embryonic lethality with single allele</td>
</tr>
<tr>
<td>PIGF</td>
<td>VEGFR-1, NP-1, NP-2</td>
<td>Placenta, lung, thyroid, goiter, cardiomyocytes</td>
<td>Angiogenesis, monocyte migration, recruitment of bone marrow-derived cells, upregulation of VEGF-A</td>
<td>Impaired neovasc. in response to MI</td>
</tr>
<tr>
<td>VEGF-B</td>
<td>VEGFR-1, NP-1</td>
<td>Cardiac, skeletal muscle, and vascular SMCs</td>
<td>Angiogenesis, recruitment of bone marrow derived cells</td>
<td>Impaired recovery from ischemia</td>
</tr>
<tr>
<td>VEGF-C</td>
<td>VEGFR-2, VEGFR-3, NP-2</td>
<td>Neuroend. organs, lung, cardiac, kidney, and vascular SMCs</td>
<td>Lymphangiogenesis and angiogenesis</td>
<td>Embryonic lethality; impaired lymph. develop.</td>
</tr>
<tr>
<td>VEGF-D</td>
<td>VEGFR-2, VEGFR-3</td>
<td>Neuroend. organs, lung, cardiac, kidney, and vascular SMCs</td>
<td>Lymphangiogenesis and angiogenesis</td>
<td>Normal</td>
</tr>
</tbody>
</table>
angiogenic factor (sFlt-1) and consists of the extracellular domain of VEGF receptor-1. It actually acts as an antagonist, binding beneficial ligands (i.e., PlGF, VEGF-A and B), sequestering them, preventing beneficial actions, and displaying an overall anti-angiogenic detrimental effect. VEGFR-2 has also been shown to be absolutely critical in cardiac remodeling. Mice treated with the VEGFR-2 decoy (which actually acts as a VEGFR trap) and subjected to a stress like trans-aortic constriction show worse fractional shortening, left ventricular dilatation and increase in myocardial fibrosis, a loss of compensatory hypertrophy, and a reduction in capillary density.

So what is the relevance of the VEGF system to cardiac disease in humans? A number of investigators have capitalized on the fact that you can measure these circulating ligands and receptors in humans.\textsuperscript{14-17} PlGF has been shown to be a predictor of adverse outcomes after myocardial infarction.\textsuperscript{14} PlGF and sFlt-1 have also been studied quite extensively as predictors of preeclampsia.\textsuperscript{17} It was found that higher sFlt-1 levels and lower PlGF levels were observed in preeclamptic patients compared to controls. We became very intrigued and asked: what is the relevance of vascular growth factors in chronic human heart failure? Therefore, we embarked on a detailed study of the translational relevance of these growth factors as biomarkers in the Penn heart failure study, which is a multicenter observational cohort of patients from Penn, Case Western, and the University of Wisconsin (Table 2). These patients were observed for the following outcomes: all-cause mortality, transplant, and ventricular assist device placement.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Mean (sd) or n, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56 (14)</td>
</tr>
<tr>
<td>Male</td>
<td>939 (67)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1034 (74)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>817 (58)</td>
</tr>
<tr>
<td>NYHA classification</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>876 (62)</td>
</tr>
<tr>
<td>III/IV</td>
<td>527 (38)</td>
</tr>
<tr>
<td>Ischemic heart failure</td>
<td>423 (30)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>33 (17)</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m(^2)</td>
<td>69 (25)</td>
</tr>
</tbody>
</table>

We found that sFlt-1 was independently associated with markers of heart failure severity, NYHA class and B-type natriuretic peptide (BNP).\textsuperscript{18} Interestingly, lower sFlt-1 levels were associated with an increase in glomerular filtration rate (GFR) and sodium. Higher PlGF levels were also associated with markers of heart failure severity and with markers of pulse pressure and hyperten-
sion. Similarly, lower levels of PlGF were associated with measures of renal function, i.e., GFR. When we looked at outcomes, we found that PlGF levels were not independently associated with adverse outcomes (Figure 1). Patients in the highest quartile PlGF had a significantly increased risk of adverse outcomes in unadjusted models, yet after we adjusted for potential compounders, this relationship was no longer significant. High sFlt-1 levels were associated with an increased risk of adverse outcomes. Patients with the highest levels of sFlt-1 had a significantly increased risk of adverse outcomes compared to those in the first quartile with an unadjusted hazard ratio

**Figure 1. PlGF Levels Not Independently Associated with Adverse Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>Unadj. HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4</td>
<td>1.9 (1.4, 2.6)</td>
<td>1.4 (0.9, 1.9)</td>
</tr>
<tr>
<td>Per</td>
<td>1.3 (1.2, 1.5)</td>
<td>1.1 (1.0, 1.3)</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age, gender, race, NYHA, diabetes, tobacco use, etiology, ICD, bi-V, ace-I/ARB, b-blocker, aldo antag, statin, BMI, log BNP, site

**Figure 2. sFlt-1 and BNP Jointly Have Strong Risk Estimates**

<table>
<thead>
<tr>
<th></th>
<th>Unadj. HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>High</td>
<td>1.4 (0.9, 2.4)</td>
<td>1.2 (0.7, 1.2)</td>
</tr>
<tr>
<td>Low</td>
<td>2.8 (1.8, 4.2)</td>
<td>2.0 (1.3, 3.1)</td>
</tr>
<tr>
<td>High</td>
<td>6.1 (4.4, 8.5)</td>
<td>2.9 (1.9, 4.2)</td>
</tr>
</tbody>
</table>

Model 1: Adjusted for age, gender, race, NYHA, diabetes, tobacco use, etiology, ICD, bi-V, ace-I/ARB, b-blocker, aldo antag, statin, BMI, log BNP, site
of 6.1 (Figure 2). After adjusting for many potential compounders, this association remained robust. We also looked at sFlt-1 and BNP in combination. We found that those patients with the highest levels of sFlt-1 and the highest levels of BNP had a significantly increased risk of adverse outcomes with an unadjusted hazard ratio of 6.1 and an adjusted hazard ratio of nearly threefold (Figure 3). We then looked at the predictive accuracy of these two markers in combination and found they had very high discriminative ability with an AUC of 0.79.

**Figure 3. sFlt-1 and BNP Jointly Improve Risk Prediction**

So what is the relevance of these PlGF and sFlt-1 cardiovascular biomarkers? We determined from our findings that sFlt-1 and PlGF are associated with renal function in chronic heart failure. PlGF is also independently associated with pulse pressure and sFlt-1 is independently associated with adverse outcomes in chronic heart failure. Together, sFlt-1 and BNP have increased predictive accuracy. How can we translate these findings to anti-VEGF therapy cardiotoxicity and how can we manage the risk of cardiotoxicity once it occurs? Despite the tremendous amount of work completed, there is still a critical need to further advance this field and develop robust biomarkers to better screen, predict, diagnose, and prognosticate.

What is the goal of biomarker use in cancer therapy cardiotoxicity? Early detection of cardiotoxic effects so we can improve prediction and identify the high risk patients; initiate early cardioprotective strategies and prevent dose interruptions; tailor a cancer therapy regimen to help decrease the cardiac risk and increase vigilance with aggressive risk factor modification; and,
improve our mechanistic understanding of the disease process. How can we use biomarkers to learn about biology and risk prediction? We have hypothesized within heart failure that we can use a diverse biomarker profile, reflective of the underlying biology as a means to better risk-stratify patients and improve our understanding of the disease process, i.e., if we measure or assess each mechanistic pathway that we believe is important in the derangement of heart failure, we can better risk stratify and risk classify our patients. We also hypothesize that our composite biomarker score would improve our ability to do so.

Within the Penn heart failure cohort, we constructed a multi-marker score comprised of the following seven markers: BNP, sFlt-1, hsCRP, ST2, troponin, uric acid, and creatinine. Those patients with the highest quartile multi-marker score had an unadjusted hazard ratio of 15 fold compared to those of the lowest quartile. After adjustment for the Seattle Heart Failure Model, which is the dominant clinical risk metric in heart failure, this association remains significant. We also looked at the discriminative ability of our multi-marker score and it had an AUC of 0.83. We then analyzed risk reclassification metrics and determined the utility of adding our multi-marker score to risk reclassification to the Seattle heart failure model. We found that approximately 19 percent of the patients were reclassified appropriately into higher risk categories.

The next question is how can we translate this knowledge to anti-angiogenesis therapy? I would hypothesize that we could better predict the risk of incident hypertension with anti-angiogenesis therapy if we had some type of marker for each of the hypothesized derangements that we believe are responsible for significant hypertension—a circulating blood marker or an imaging parameter—i.e., decrease in capillary density and profusion, thyroid dysfunction, neurohormonal alteration, cardiac renal interaction, decrease in nitric oxide production, and a measure of vascular stiffness and smooth muscle effects. Similarly, could we do the same with cardiac dysfunction via the hypothesized mechanisms of vascular inhibition and hypoxia, endothelial/cardiomyocyte stress, pro-apoptotic effect, cardiac renal interaction, mitochondrial dysfunction, AMP-activated protein kinase inhibition, and an increase in LV afterload? If we had a precise measure of each of these derangements, could we better predict the risk?

In order to answer these questions, infrastructure is necessary, thus the cardiovascular effects of sunitinib therapy study. Our goal is to provide mechanistic and translational insight into the dysregulation of pathways with sunitinib, using comprehensive imaging and biomarker tools and the objective is to determine if baseline or early changes of markers of cardiomyocyte endothelial cell function or ventricular vascular function are predictors of sunitinib cardiotoxicity. Our exposures are measures of cardiomyocyte endothelial cell function and ventricular vascular function and the outcomes we are following are LV dysfunction, heart failure, and hypertension. This is a multisite study, building upon our heart failure collaborations, involving Penn, Vanderbilt, Case Western, and University of Wisconsin. We’re targeting recruitment of 18 subjects at each site for a total of 72 and specifically want renal cell patients who are newly initiating sunitinib.

Our first goal is to determine a relationship between circulating markers of vascular growth and
cardiomyocyte/endothelial cell function and incident risk of cardiotoxicity with exposure to sunitinib. The hypothesis is that circulating growth factors reflective of vascular growth, endothelial cell function, and cardiomyocyte stress are early predictors of cardiotoxicity. Learning from our chronic heart failure work, immediate questions would be, what is the association between PIGF and incident risk of hypertension, heart failure and LV dysfunction? Or could we construct a multi-marker paradigm to better predict risk of these outcomes?

Our second goal is designed to determine the effect of sunitinib on cardiac remodeling, contractility, and vascular human hemodynamics using detailed tonometry and echocardiography. The hypothesis is that vascular function and mechanical load are important determinants of cardiac function and remodeling.

There are multiple potential implications for this work that include: defining circulating markers that are robust, mechanistic predictors, so that we may implement cardio-protective medications early, prevent dose interruption or cessation of therapy, and tailor cancer therapy better; determining what changes in vascular function actually occur so that we may better treat patients with a more appropriate choice of anti-hypertensive medicine; and, finally, discovering if changes in ventricular vascular coupling and myocardial strain occur to determine if these are robust predictors of cardiac dysfunction.

References


Accurately Measuring and Reporting Cardiotoxicity

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“We need accurate trial reporting and, as a profession, not tolerate under reporting... which has clearly led to an under recognition of the cardiotoxicity of this drug.”

—Ron M. Witteles, MD, FACC

Our discussion of accurately measuring and reporting cardiotoxicity will be centered around four hypotheses. Hypothesis one: product labeling is often a mess. Hypothesis two: cardiotoxicity definitions in Common Terminology Criteria for Adverse Events (CTCAE) 4.0 are in desperate need for reform. Hypothesis three: those who don’t learn from history are doomed to repeat it. Hypothesis four: all of this matters.

The first hypothesis is that product labeling is often a mess. For example, the doxorubicin label today reads: “Treatment of doxorubicin induced congestive heart failure includes the use of digitalis, diuretics, afterload reducers such as ACE inhibitors, low salt diet, and bed rest. Such intervention may relieve symptoms and improve the functional status of the patients.” In 2011, the official documentation still tells us that state of the art treatment for heart failure is bed rest. The labeling goes on to say: “The probability of developing impaired myocardial function is estimated to be 300 mg/m² 1-2%, 400 mg/m² 3-5%, 450 mg/m² 5-8%, and 500 mg/m² 6-20%.”
In 1979, over 4000 patients who had received doxorubicin were examined and doxorubicin-induced congestive heart failure (CHF) was defined as clinical signs and symptoms of congestive heart failure believed to be secondary to doxorubicin.² This definition came from the clinician who was almost always an oncologist. The overall incidence of doxorubicin-induced CHF was 2% and the inflection point occurred at 550 mg/m² cumulative dose. This means that below 550 mg/m² cumulative dose, the rate was very low (7%).

Swain and colleagues performed an analysis of the placebo-arms of three dexrazoxane trials so that the unadulterated effects of anthracyclines could be seen.³ The data showed a significant drop in left ventricular (LV) systolic function. While looking for cardiotoxicity they were frequently monitoring ejection fraction (EF) and once a patient achieved a dose of 150 mg/m², they were checking every 50 mg/m², so the data is good. At 350 mg/m² the inflection point is > 16% and at 550 mg/m², the inflection point is 65%. Patients would have much more pause to use higher doses of anthracyclines or would at least look more cautiously for cardiotoxicity.

The Sutent® labeling was updated in May of 2011 and it says that 27% of patients in the treatment-naïve RCC study had EFs below the lower limit of normal.⁴ The labeling then says later in the very same paragraph that LV dysfunction is present in 1%. Now I don’t know about you, but to me LV dysfunction and EF below lower limit of normal are the same thing. How is a statement like this allowed in the labeling?

Hypothesis two is that cardiotoxicity definitions in CTCAE 4.0 are in desperate need of reform. If there is one thing that would probably have a greater impact than anything else, it is to reform CTCAE 4.0 for cardiotoxicity definitions. I mentioned this last year, so perhaps there’s impetus for something to happen now. CTCAE does deserve praise for its efforts in standardizing definitions for oncology clinical trials as this is far ahead of anything we have in cardiology. It is incredible that cardiology has no standard way of defining toxicity. When CTCAE moved from 3.0 to 4.0, there were some well-intentioned changes in the definitions of cardiac toxicity with the goal of improving cardiac monitoring. It is questionable as to whether or not the goal was realized.

CTCAE v3.0 came out in 2006 and in this version all the cardiac events were located under “Cardiac General” or “Cardiac Arrhythmias”⁵ CTCAE v3.0 did have elevated troponins in the criteria, yet it wasn’t quite right (Table 1). Troponin I and troponin T had very different classifications. Troponin T had this level of 0.2 ng/mL and if it was above that, then it was considered a grade four event—remember that grade four events are supposed to be life-threatening consequences. In fact, grade four is just below grade five which is death. So classifying that as grade four may be a little much.

Looking at LV dysfunction (Table 2), they have separated diastolic and systolic dysfunction. Diastolic dysfunction is a bit of a mess, even in the cardiology world, so it became even harder to define for CTCAE. Systolic dysfunction has various EF measurements—50-59% for grade one, 40-49 percent for grade two, 20-39 percent for grade three, and < 20% for grade four.

So there were a few problems with CTCAE 3.0 which were in need of reform: the troponin
inconsistency, the diastolic dysfunction, the definition for grade one going up to 59% was strange because most of us define normal EF as > 55%—strange that grade one dysfunction would be 59%. Some of the positives of CTCAE 3.0 is all of the cardiac toxicities were located in one section. You opened up to cardiac general and there it was. If the LV dropped, it was clear what it should be called—grade one, two, three or four, based on what the EF was and there was a clear

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>CARDIAC GENERAL</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac ischemia/infarction</td>
<td>Cardiac ischemia/infarction</td>
<td>Asymptomatic arterial narrowing without ischemia</td>
<td>Asymptomatic and testing suggesting ischemia; stable angina</td>
<td>Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated</td>
<td>Acute myocardial infarction</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Cardiac troponin I (cTnl)</td>
<td>cTnl</td>
<td>—</td>
<td>—</td>
<td>Levels consistent with unstable angina as defined by the manufacturer</td>
<td>Levels consistent with myocardial infarction as defined by the manufacturer</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Cardiac troponin T (cTnT)</td>
<td>cTnT</td>
<td>0.03 – &lt; 0.05 ng/mL</td>
<td>0.05 – &lt; 0.1 ng/mL</td>
<td>0.1 – &lt; 0.2 ng/mL</td>
<td>0.2 ng/mL</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary arrest, cause unknown (non-fatal)</td>
<td>Cardiopulmonary arrest</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Life-threatening</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. General Cardiac Troponin I and T Definitions (CTCAE v3.0)**

**REMARKS:** Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death:
1. A CTCAE term associated with Grade 5.
2. A CTCAE ‘Other (Specify______)’ within any CATEGORY.
3. Death not associated with CTCAE term – Select in the DEATH CATEGORY.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Short Name</th>
<th>Grade 1</th>
<th>CARDIAC GENERAL</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Hypotension</td>
<td>Changes; intervention not indicated</td>
<td>Brief (&lt; 24 hours) fluid replacement or other therapy; no physiologic consequences</td>
<td>Sustained (≥ 24 hours) therapy; resolves without persisting physiologic consequences</td>
<td>Shock (e.g. acidemia, impairment of vital organ function)</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Left ventricular diastolic dysfunction</td>
<td>Left ventricular diastolic dysfunction</td>
<td>Asymptomatic diagnostic finding; intervention not indicated</td>
<td>Asymptomatic; intervention indicated</td>
<td>Symptomatic CHF responsive to intervention</td>
<td>Refractory CHF; poorly controlled; intervention such as ventricular assist device or heart transplant indicated</td>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td>Left ventricular systolic dysfunction</td>
<td>Asymptomatic, resting ejection fraction (EF) &lt; 60–50%; shortening fraction (SF) &lt; 30–24%</td>
<td>Asymptomatic, resting EF &lt; 50–40%; SF &lt; 24–15%</td>
<td>Symptomatic CHF responsive to intervention EF &lt; 40–20%; SF &lt; 15%</td>
<td>Refractory CHF or poorly controlled; EF &lt; 20%; intervention such as ventricular assist device, ventricular reduction surgery or heart transplant indicated</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. General Cardiac Left Ventricular Dysfunction Definitions (CTCAE v3.0)**

inconsistency, the diastolic dysfunction, the definition for grade one going up to 59% was strange because most of us define normal EF as > 55%—strange that grade one dysfunction would be 59%. Some of the positives of CTCAE 3.0 is all of the cardiac toxicities were located in one section. You opened up to cardiac general and there it was. If the LV dropped, it was clear what it should be called—grade one, two, three or four, based on what the EF was and there was a clear
description of the grading. Other than the grade one definition going up to 59%, I would argue that the grades of toxicity were fairly reasonable.

Now when we went to CTCAE 4.0 we took a step backwards: the number of cardiac toxicity terms increased from 15 to 36; three different ways of grading the same event were created; and LV systolic dysfunction was misdefined. The definition says “a disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume.” Now that might be a reasonable definition of heart failure, but it is not a reasonable definition of LV systolic dysfunction.

For example, consider the case of a patient who has an asymptomatic drop of EF from 60% to 35%, and ask how the responsible oncologist should grade this according to the current criteria. The oncologist will turn to the table of contents, find cardiac disorders, go to LV systolic dysfunction, and then call it grade zero because there are no grade one or grade two events listed and by the time you get to grade three, it has to be symptomatic. Or perhaps the oncologist turns to heart failure and now classifies it as a grade one event because it is an asymptomatic cardiac imaging abnormality. We have a problem now because the same event can be considered grade zero or grade one. It gets worse. If the oncologist selects “investigations” from the table of contents, then the LVEF drop will be considered a grade three event. So the same event by three different oncologists could be graded grade zero, grade one, or grade three. If the goal is to have consistent definitions, then we have failed.

There is another very important caveat: When does an event count? The answer: it counts when the site investigator reports it. Now this may make sense if you’re talking about a subjective historical point, but it doesn’t make any sense at all when we’re talking about an objective laboratory or imaging finding. For example, if the patient is neutropenic, the patient is neutropenic as long as the lab got it right, whether the local investigator fills out a case report form or not. Similarly, if there’s a drop in LVEF, so long as it is indeed a real drop in LVEF, it should not matter if the local investigator fills out the form, as long as the central investigators have access to the data.

One more very important caveat. How likely is the event considered to be related to the intervention being studied—the so-called treatment related adverse event? This is an enormous can of worms if we are dealing with an unexpected side effect. If it is an expected side effect, then that is fine. But if it’s unexpected, as often a drop in LVEF is, then the local investigators are likely to call this non-treatment related which often means that it never existed.

Hypothesis three is those who don’t learn from history are doomed to repeat it. With this, I want to examine sunitinib which was approved in 2007 by the FDA based on two phase III clinical trials. It’s currently under investigation for more than 30 tumor types in over 300 clinical trials. It would be fair to call it the oncologic success story of the last decade and we can learn a lot from it.

The story begins in 2005 with this phase I trial being published. In phase I, patients with refractory or resistant acute myeloid leukemia (n=15) are treated with sunitinib. Two of the 15 patients, without any prospective imaging in this trial, developed heart failure and one of them
died from heart failure deemed to be possibly related to the study drug. Phase two data are published in 2006.\textsuperscript{8} In phase II, patients with renal cell carcinoma (n=63) are treated with sunitinib. All patients had a normal LVEF at the start. In 11\% of patients there were LVEF declines to below normal on two or more specimens and 6\% of patients had to be removed from the protocol because of declines in ejection fraction. So reasonable concern after phase I and II.

The first of the phase III studies appeared in late 2006.\textsuperscript{9} Patients with GI stromal tumors (n=312) were randomized for sunitinib or placebo. Cardiac monitoring with multi-gated acquisition scan (MUGA) was performed at the start and finish of every cycle of sunitinib. However, if you turn to the article, you will not find the MUGA data anywhere in it. You will find a line in the article that reads, “We noted no evidence of a systemic mean decrease in left ventricular ejection fraction in either treatment group, and no patients reported to have had clinical evidence of congestive heart failure.”\textsuperscript{9} This reads like there is absolutely no reason to suspect that this drug has cardiac toxicity issues. Three months later, the sunitinib label is published and quoting the same study it notes that 11\% of sunitinib patients versus 3\% of placebo patients had treatment-emergent LVEF drops to below the lower limit of normal.\textsuperscript{10} Additionally, three patients on sunitinib had grade three reductions in LV systolic function and two of them died without receiving further study drug. These are very different ways to present this information.

The second phase III study appeared in January, 2007.\textsuperscript{11} Patients with renal cell carcinoma (n=750) were randomized to receive sunitinib or interferon alfa. They had normal LVEF at baseline. This article listed LVEF in the adverse event table and if we look closer, we find that 10\% of sunitinib patients had a decline in LVEF versus 3\% on interferon. Once again a strange thing happens when the label is published quoting the same study.\textsuperscript{12} The patients who had LVEF values below the lower limit of normal is no longer 10\%, it is 21\%. This is where that strange comment comes from—that LV dysfunction is in only 1\% of patients. In the updates four years later, the percent has grown. It was 10\% when the study came out, 21\% a month later, and now 27\%.\textsuperscript{13} This, by the way, is not follow up data. This is the data from the same study and it is just mysteriously continuing to grow. Who knows where it will be four years from now.

The third phase III trial data was published in 2011.\textsuperscript{14} Patients with pancreatic neuroendocrine tumors (n=171) were randomized to receive sunitinib or placebo. They all had normal baseline LVEFs and there was no cardiac imaging built into the study. After all of the data from phase I, II, and two studies from phase III were published and known cardiac changes were noted, no cardiac imaging was built in to the third phase III study. The only thing I can conclude is that it was so downplayed in the two publications that it was just assumed to not be an issue. Now despite the fact that no cardiac imaging was built in, 2 out of 83 patients died from treatment related heart failure, yet if you read the article, it will note only one patient died of treatment-emergent heart failure. If we want the truth, we have to go and look in the fine print of the label and find out that it was actually 2 out of 83 patients who died from heart failure.

So how could any of this happen? This is the author’s explanation for the lack of inclusion
in the table of adverse events in that article. “The table summarizes the treatment related adverse events that occurred with a frequency of > 5% on sunitinib compared with placebo. The LVEF declines were not reported in this table since the frequency did not meet the criteria (6.4% versus 2%). The product label, on the other hand, reports the frequency (11% for sunitinib versus 3% for placebo) of LVEF declines to below the lower limit of normal as measured by the MUGA scan.” So it was almost a fourfold increase in the rate of LVEF declines, yet the investigators felt no compunction to report this in the publication because so many weren’t called treatment-related adverse events.

How could this happen? How does it grow from 10% to 21%? In our assessment, treatment-related adverse events, as reported by the investigators, were clinically more informative and relevant for the purpose of journal publication than MUGA data. The FDA, on the other hand, wanted the actual data. If the *Lancet* and *New England Journal of Medicine* studies are examined closely, then the result they were reporting is treatment-related adverse effects.

The argument is not that the MUGA data was incorrect. Rather the argument is that if a site investigator doesn’t report an LVEF drop as an adverse event, or considers it non-treatment related, there is no responsibility on the investigator to report it in the publication even when the message is clear. Note that the investigators had access to all of this data—this was the data submitted months earlier to the FDA. The fact that a statement like “no systemic mean decrease in ejection fraction” appeared in the publication seems that it is clearly intended to mislead.

Hypothesis four is that all of this matters. It matters when we use old data to guide treatment decisions for doxorubicin. It matters when we downplay that almost everybody on sunitinib has an LVEF drop. It matters when we look at Stanford data from the first 48 patients who got sunitinib, most of whom did not have cardiac monitoring, and 7 developed symptomatic heart failure and 2 of them died from it. It matters when we look at a meta-analysis and there is an increased risk of high-grade heart failure with sunitinib. In the same study, investigators noted that in trials where there was cardiac screening, you had higher rates of LVEF drops, high-grade heart failure, and symptomatic heart failure, than in studies without screening. One can argue that screening is not necessary for symptomatic heart failure, yet you are twice as likely to call an event symptomatic heart failure if you do the screening because you know that dyspnea may not be due to the lung metastasis and that maybe it’s due to the LVEF drop.

In conclusion, what do we need to do? We need to update the labeling as it is embarrassing for the doxorubicin label to read as it does now and it is embarrassing to say that 27% have LVEFs below normal, but only 1% have LV dysfunction. We need to reform CTCAE now—we cannot have a system where the same event can have three different grades of toxicity, even by well-intentioned investigators. We should not rely on site investigators for reporting objective measures when that data is available. We should consider all adverse events and not hide behind whether they are called treatment related or not. We should build routine cardiac imaging into more trials and require it for a third phase III study. We need accurate trial reporting and, as a profession, not
tolerate under reporting, as with sunitinib, which has clearly led to an underrecognition of the cardiotoxicity of this drug. I’ll close with this quote by George Orwell, which is as appropriate today as it was in 1945. Orwell said, “People can foresee the future only when it coincides with their own wishes, and the most grossly obvious facts can be ignored when they’re unwelcome.”

References

5. Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0; Department of Health and Human Services; Publish Date August 9, 2006.
6. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0; Department of Health and Human Services; Published May 28, 2009.
15. Quoted from response to letter from *The Lancet* by Demetri, Motzer, and Baumm (Pfizer).
QT Monitoring During Oncology Trials: Can We Realistically Expect to Learn Anything?
Carlo M. Cipolla, MD
Cardiology Division, European Institute of Oncology, Milan, Italy

“We believe that the future of early detection of cardiac damage will be in the intracellular intramitochondrial biomarkers.”
—Carlo M. Cipolla, MD

A French cardiologist discovered Torsade de Pointes (TdP) in 1966 and in Bethesda, Maryland, in 1989, physicians at the National Naval Medical Center recognized for the first time that QT prolongation was associated with terfinadine (Figure 1).1

The FDA and other health agencies are increasing their regulatory focus on QTc prolongation assessment for non-antiarrhythmic drugs. Issues concerning specific QT studies for oncology are not clearly addressed in ICH E14 guidance document. The discontinuation criteria are marked prolongation of the QT, QTc interval during treatment with the study drug and the threshold for potential discontinuation are increases in QT/QTc to > 500 milliseconds or an > 60 milliseconds over baseline.

The decision by a physician to use a drug, or by a regulatory agency to approve one, is predicated on the assumption that the benefits of the therapy outweigh the risks. As an example, arsenic trioxide represents an interesting example of this balance. Although this drug is known to induce QTc prolongation and potentially a TdP, it is also uniquely effective in relapsed acute promyelocytic leukemia.
The classic background tells us anti-cancer drugs may prolong QT interval, increasing the risk of serious ventricular arrhythmias and sudden death. Cancer patients are considered at increased risk of life-threatening arrhythmias because of additional predisposing risk factors (e.g., electrolyte abnormalities, starvation and medications). That’s a classical background.

Most of the data have been derived from clinical trials in which patients with a baseline long QT have systematically been excluded. Information on the true incidence of a baseline long QT interval, and on its possible prolongation during anti-cancer therapy in clinical practice are still lacking. So we started the so-called “Anti-QTc crusade.”

What does it mean? We studied 1300 records from 2000-2010 of unselected patients previously treated with computed tomography. The echocardiograms were corrected for heart rate by Bazett’s formula as defined prolonged QT > 440 millisecond for males, and > 460 milliseconds for females. Cardiac events were defined as sudden death, non-sustained ventricular tachycardia, ventricular tachycardia, TdP, and syncope. We analyzed over 3800 echocardiograms and almost 1300 patients had at least one echocardiogram, more than 900 had two echocardiograms, more than 500 had three echocardiograms, and so forth.

So in the real world, when a patient starts chemotherapy, adding or not adding before chemotherapy, what is the situation? The situation is that 88% of patients have a normal QTc and 12% of the patients have prolonged QTc—which is a high percentage. Let’s see why we have 12% of prolonged QTc in a patient that is going to start chemotherapy. Because of previous chemotherapy? No, not significant. Because of previous anthracyclines? No, not significant. The significance we find is if this patient has cardiovascular disease or previous cardiovascular therapy.

Other things that are important are, in this setting, the presence of coronary heart disease, slight hypertension, and ventricular arrhythmias. In regards to medications, it is curious to say that only ACE inhibitors and angiotension receptor blockers, and diuretics can influence the prolonged QTc.

What happens to patients that have multiple echocardiograms during chemotherapy? That is dramatic. You can see an increase in the QTc from 420 to 440 milliseconds in all the patients. That is dramatic. During chemotherapy, all the patients progressively increased QTc by 20 milliseconds. So what happens to these patients? The 700 patients that had normal QTc continued having normal QTc in almost 85% of the cases during chemotherapy. Between 15–20% of the patients with normal QTc in the baseline prolonged the QTc and 3 of them increased > 60 milliseconds.

Patients with a prolonged QTc at baseline is curious as they usually normalize QTc during chemotherapy (at least 35%). Some are still prolonged slightly, the QTc, and 9 patients had prolongation of the QTc of > 60 seconds. Why these changes? We did not see major cardiac vascular events. Just one case of non-sustained ventricular tachycardia in the setting of normal QTc and there was nothing to report.

In conclusion, we say a long QTc is almost influential if you frequently observe oncologic patients receiving anti-cancer therapy. Both a baseline long QTc and its weak prolongation during anti-cancer therapy seem associated with the occurrence of nothing. No life-threatening arrhyth-
mias. Remember that cardiological comorbidity, at least in our hospital, is 42% and these are confusing factors since the presence of hypertension and cardiological drugs can modify more than the presence of previous chemotherapy the QTc. This is why we look at the use of biomarkers, troponin, BNP, and mitochondria. We believe that the future of early detection of cardiac damage will be in the intracellular intramitochondrial biomarkers.

References

**Case Studies in CardiOncology**

Alan T. Kono, MD

Director, Congestive Heart Failure Clinic, Dartmouth-Hitchcock Medical Center, Lebanon, NH

“Our increasing understanding of how cancer therapies can affect the cardiovascular system creates a unique and challenging environment that can result in competing therapeutic goals.”

—Alan T. Kono, MD

In the past, heart disease was the number one killer in the United States and it has only been recently that oncology mortality has surpassed cardiovascular disease, especially in the younger population. If we compare the high risk of mortality in patients with cardiomyopathy to the mortality in patients with breast cancer, the results look very similar. The other issue to consider is when patients are being treated and where they are in their disease. So how do cardiologists and oncologists collaborate and create synergy between two subspecialties that are treating the same patient?

**First case:** An athletic 45-year-old female professional who ran half-marathons noticed rectal bleeding in 2007 and underwent a colonoscopy that was described as normal. The rectal bleeding continued for two years, and the patient saw a new primary care physician, who sent her to a gastroenterologist. A repeat colonoscopy demonstrated a rectal mass, and the biopsy shows differentiated rectal carcinoma, stage 2A, T3N0M0. A CT scan and ultrasound of the abdomen were normal. The plan of care included neoadjuvant chemotherapy followed by radiotherapy and surgery, which was a very aggressive approach. This patient noted new chest discomfort and dyspnea with exercise a few days after initiation of capecitabine. The symptoms lasted for about
20 minutes and she had recurrent symptoms with exertion, so she decided to see her physician, who did an electrocardiogram, which was normal, with no acute ST/T-wave changes, and no QT prolongation. The chemotherapy was held and a stress echocardiogram was performed, which was described as normal. The patient actually went 15 minutes on the Bruce Protocol and her left ventricular ejection fraction (LVEF) was 60%. She described no symptoms and the capecitabine was restarted. The patient had a repeat stress test, now only going 12 minutes on the Bruce Protocol, and the electrocardiogram was normal. After reaching Stage IV, she developed mild chest discomfort and ST elevations at peak stress, yet on recovery the electrocardiogram returned to normal. The conclusion of the stress test was that there was angina in recovery, indeterminate ischemic electrocardiogram changes, and the probability of ischemia is low, and there was a side comment saying there were transient ST elevations and questionable spasm.

Cardiologist #1 recommends amlodipine, to avoid strenuous exercise, go to the emergency room if chest pain recurs, and repeat the treadmill next week on medical therapy. While on amlodipine and capecitabine, she exercised 11 minutes on the Bruce Protocol, which is four minutes less than just three weeks earlier. Blood pressure (BP) response was normal, some premature ventricular contractions were noted, yet she had no symptoms or electrocardiogram changes; and there was a slight improvement in her LVEF (i.e., 60–65%) suggesting that she had some cardiac reserve.

Cardiologist #2 recommended no further chemotherapy because of the concerns about cardiac effects of the medicine, and to avoid strenuous exercise. The patient and her oncologist decided to finish the capecitabine. She had no symptoms, yet she led a very sedentary lifestyle and started becoming depressed and unhappy with her course of care. She then received radiotherapy and was referred to the advanced heart failure cardiomyopathy clinic.

The question being asked of us: what is the right decision regarding the risk of continuing the capecitabine or a 5FU adjuvant chemotherapy after surgery? This patient had no migraine headaches, no Raynaud’s, and no other forms of vasospastic disease. Her LDL cholesterol was mildly elevated, she is a non-smoker, and she normally drinks a pot of coffee a day. She had a family history of obesity, hypertension, hyperlipidemia, early myocardial infarction, and heart failure. After a lengthy discussion we decided to proceed with cardiac catheterization an except for a non-dominant right coronary artery, angiography demonstrated normal coronary arteries and LVEF. So, who would proceed with chemotherapy? Who would choose alternative therapy? Who would choose additional therapy? How would you support her through a re-challenge of chemotherapy? Her Oncogene score was 47, which predicted an approximate 20% chance of recurrence in three years.

This case raises the question of who makes shared decisions and what is the process of decision making? This patient had two primary care physicians, two oncologists, a radiation oncologist, a surgical oncologist, two general cardiologists, and a heart failure specialist with interest in cardiology. What kinds of methods of communication do we use? This patient not only had a formal
consult with my recommendations, she had a total of 14 emails between providers, four phone calls with the patient, and five phone calls with providers to include calls to other institutions.

**Second case.** This 48-year-old female presented with breast cancer in 2009 that was ER/PR(+), HER-2(-), and lymph node positive for invasive ductal carcinoma. Her initial therapy was under a research protocol and she received six cycles of AC—the total dose being 360 mg/m². It was followed by weekly paclitaxel, then tamoxifen 3 months later, and then she had radiation to the left chest 2 months after the tamoxifen started. After cycle number six, during her paclitaxel, she developed chest pain and had a positive troponin T. While on the inpatient oncology service, she was seen by the inpatient general cardiology consult service who recommended cardiac catheterization. Her coronary arteries were normal and serial echocardiograms were performed during her entire therapy demonstrating normal LVEF and normal volumes. Unfortunately, a year and a half later she was diagnosed with acute lymphoblastic leukemia.

A cardio-oncology consult was requested. Her baseline LVEF was 72% and normal chamber sizes. We believed this patient was at high risk for additional myeloablative therapy with AC-based chemotherapy due to the positive troponin, her prior total AC dose, and the fact that she had radiotherapy to her left chest. Our recommendations included monitoring the troponin, NT-proBNP, as well as serial echocardiogram before each cycle. We also recommended adding an ACE inhibitor and that we would follow the patient along with the oncology service.

The oncologists were the primary providers and they felt strongly to proceed with chemotherapy, so an additional 240 mg were given for a total dose of 590 mg. Troponin and NT-proBNP were monitored during cycle one and they were normal. No echocardiogram or biomarkers were performed for cycle two. Three months later, she presented with acute decompensated heart failure, new atrial fibrillation and atrial flutter, and required a critical care unit admission. She had a positive troponin, and her NT-proBNP went from 138 to 11,800 pg/mL. Her previous echocardiogram revealed normal chamber sizes and function with LVEF of 72%. Three months later, her LVEF had deteriorated to 25%.

This case illustrated that there was no coordination of care between the services. The new hematology/oncology inpatient attending was not aware of the prior heart failure service consult or recommendations and the heart failure service wasn’t informed of her second admission. Therefore, managing a complex patient can be challenging when there are silos of medical care. We are becoming very sub-specialized with our care and we have these silos of care between sub-specialists who have the common interest of the patient, but perhaps different timelines and targets. It is further complicated when a patient comes to the hospital because now we have the inpatient oncology service, an inpatient cardiology consult service, and the hospitalists service. Who’s managing this patient?

Cardiology has become super subspecialized in that we have invasive, interventional, non-invasive, electrophysiology, heart failure and transplant, and preventive sub-specialities. In hematology/oncology, we have hematology, medical and surgical oncology, radiation oncology,
and now interventional oncology and disease specific oncologists. There is acute care in cardiology that manages myocardial infarction, acute heart failure, arrhythmias and so forth. There is acute care in oncology that deals with acute myeloid leukemia, blast crisis, and lymphomas and complications of their therapies. And of course, there is subacute and chronic care with cardiology and oncology.

Cardiovascular treatments include invasive/interventional, cardiothoracic surgery, pharmacotherapy, devices, hybrid procedures and palliative care. Similarly in oncology, we have interventional, radiation, surgery, pharmacotherapy, and palliative care. So how do we mix these two sub-specialties together and how do we best discuss care of these patients? It is imperative that we promote a multidisciplinary approach with shared decision making and effective communication. This may be more challenging to implement. An example in our institution: we had a tumor board presentation and delivered a didactic session entitled, “Why is cardiology in the room?” as it was a new culture to have non-oncologists in the same room. How do we deliver therapy in a situation where we have two very specialized sub-specialties? A patient-centered care model with informed, engaged patients who are active in their decision making and understand their disease process, along with a coordinated team that’s knowledgeable and following that patient for the duration of their illness while using evidence based medicine to treat might be ideal. This is called the medical home, yet we could utilize different models and have a specialty medical home or a medical home where the primary care provider and a specialist are the directors of care.

Based on well established models of care such as the medical home, the main components are:

1) Productive interactions centered around the engaged and informed patient—those patients who are motivated, informed, skillful, and confident to make effective decisions about their health and management.

2) A prepared practice team that are ready with patient information, decision support, and resources necessary to deliver high quality care at the time of interaction.

3) A tailored clinical management step protocol to follow these patients with routine biomarkers or imaging and collaborative goal setting and problem solving.

4) Active, sustained follow up and coordination of care.

All of this takes effective communication. Possible methods of effective communication include:

1) A team huddle so clinicians actually get in the same room and discuss a patient in order to come up with a care plan for that day or perhaps for the course of therapy.

2) A cardiologist as a guest at the tumor board, member of the HemOnc P&T committee, or presenter at HemOnc grand rounds.

3) Conducting combined cardio-oncology grand rounds.

4) Conducting a combined cancer survivor cardiac risk assessment, where oncologists and cardiologists help in the assessment of high-risk patients.

5) Basic science and clinical research collaboration.
Finally, in order to promote awareness of the special needs of the cardioncology patient, it is important to educate our cardiology colleagues and trainees to involve oncology when an oncology patient is on the cardiology floor; and educate our oncology colleagues and trainees to involve cardiology when a cardiac patient is on the oncology floor.

These two cases help illustrate some of the barriers in managing complex patients who have separate, yet interrelated, disease processes each with their independent guarded prognosis. Our increasing understanding of how cancer therapies can affect the cardiovascular system creates a unique and challenging environment that can result in competing therapeutic goals. By increasing awareness and understanding of the shared decision making model and medical home may help build communities of shared expertise around patient-centered care. We want to collect and connect the silos. We want to have more conversations in the same room so there is synergy and collaboration. We want to move the field from “we don’t know” or “it’s been reported” to “we see this” and “we know this.”

Can Cardiac Biomarkers Provide Better Information for the Detection of Cardiotoxicity?
Maria Teresa Sandri, MD
Medical Director, Division of Laboratory Medicine, European Institute of Oncology, Milan, Italy

“New high-sensitivity troponin allows for the detection of very small cardiac damage and the studies available in patients with different cardiac disease suggest that this is a real improvement not only from the technical point of view but also from the clinical point of view, yet there are no conclusive data on the impact of these high-sensitivity troponins in the prediction of chemotherapy-induced cardiotoxicity.”

—Maria Teresa Sandri, MD

Ten years ago we could demonstrate that increases in troponin I after the administration of high-dose chemotherapy could predict the development of left ventricular dysfunction. In fact, we analyzed 204 patients treated with high-dose chemotherapy and could measure the troponin often during the administration of therapy. In 32% of the patients, we had one or more increases in troponin during the administration of the chemotherapy.

When we looked at the left ventricular ejection fraction (LVEF) during follow up, a slight decrease in function could be detected in the first month and then it decreased significantly in patients in which an increase in troponin was observed. We could demonstrate that the higher the increase of troponin, the higher the reduction in LVEF.

A few years later, we tried to combine different troponin results to evaluate the risk of our patients developing cardiotoxicity or a cardiac event. We analyzed 703 patients, again treated with...
high-dose chemotherapy, and we had quite a long follow up with these patients (i.e., > 3 years). The main objective was to record the occurrence of major adverse cardiac events.

We measured troponin in the period before, soon after, and one month after the administration of high-dose chemotherapy. The early determination was the measurement during or just after the chemotherapy and a late determination was the measurement one month after the completion of chemotherapy.

Combining these two results, we had three different patterns: 70% who were always negative, 9% who had positive troponin during or just after the administration of the chemotherapy and one month later, and 21% positive troponin during or soon after the administration of the chemotherapy and a negative troponin one month at the end. These different patterns allowed us to subdivide patients into three groups each with a different risk of developing a cardiac event. More than 70% of patients had a low risk of developing a major adverse cardiac event, while the high-risk patients (9%) tested positive for troponin early and late and these were the patients that had the majority of adverse cardiac events.

We thought the information on troponin could help prevent cardiotoxicity. We evaluated troponin in 473 patients and detected a positive troponin during or soon after the administration of the chemotherapy in 114. These patients were randomized for treatment with enalapril or control group. The enalapril was started one month after the chemotherapy completion and continued for one year. We had a decrease in LVEF, and detected a decrease only in the control group, while inpatients receiving the enalapril and having a positive troponin at the enrollment, didn’t develop any decrease in LVEF (Table 1). Just one patient in the enalapril group had an arrhythmia during the one-year follow up while in the control group had nearly all the cardiac adverse events.

Other authors are now suggesting that cardiac troponin is the most useful translational safety biomarker in the early detection of cardiotoxicity. This is obvious because we know that tropo-

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<tr>
<th>Table 1. Cardiac Events in the Study Groups³</th>
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<tr>
<td>Total (n=114),</td>
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<td>n(%)</td>
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<tr>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Sudden death</td>
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<tr>
<td>Cardiac death</td>
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<tr>
<td>Acute pulmonary edema</td>
</tr>
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<td>Heart failure</td>
</tr>
<tr>
<td>Arrhythmias requiring treatment</td>
</tr>
<tr>
<td>Cumulative events</td>
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*Fisher exact test.
nins have a high cardiac specificity and a high sensitivity. They do not suffer from inter-observer variability as other systems do that are used to monitor patients, are much less expensive than other systems, and can be easily repeated during follow up. A useful approach could be to assess baseline biomarker concentrations in every patient and to measure them periodically during and after a potentially cardiotoxic cardiac cancer treatment and increases in these biomarkers may be a signal that underlines the need for further cardiac assessment.\(^5\)

So, do we need to improve? We have a very good marker which has a very high negative predictive value—a minimal chance of developing an adverse cardiac event.\(^4\) On the other hand, we have some problems with the positive predictive value. There are some patients in which we could detect increases in troponin and do not develop any cardiac dysfunction. Keep in mind that not all troponin assays are created equal and this is mainly due to the fact that there is no common reference material which can be used by the different manufacturers to calibrate their new assay. The assays are different because the assay format is different—different antibodies (e.g., monoclonal, polyclonal, two antibodies, three antibodies; the epitope location on troponin molecule which is used to design the assay; the specificity of the antibody) and the method of detection. Few contemporary assays meet the quality specifications required by the 2007 definition of acute myocardial infarction which states that the troponin test used for these patients should have total imprecision (coefficient of variation [CV] at 99th percentile upper reference level, equal to or less than 10%).

The vast majority of contemporary tests do not meet the criteria, yet they have a CV 10–20% (Table 2).\(^6\) Up to 20% these tests have been demonstrated to be useful and clinically acceptable in the management of acute myocardial infarction (AMI). In any case, there was a push for the manufacturers to develop new assays able to detect with high precision a very low concentration of troponin. The development of cardiac biomarkers is a 60-year story, yet troponin T and troponin I have become the key biomarkers for the diagnosis of AMI and for risk stratification in only the last 10-12 years. We are now witnessing the development of more sensitive and precise assays able to detect extremely low concentrations of troponin in the blood.

So how can we define this new high-sensitivity troponin? There is no complete and unique definition, yet let’s say that these assays are able to detect a level of troponin also in healthy subjects which means above the limit of detection of the assay and, of course, below the upper reference range. The percentage of patients that should have troponin detected is still a matter of question. There has been proposed a classification of this high-sensitivity troponin looking at the percentage of normal subjects that test positive with this assay, yet it is still to be accepted by the international community (Table 3).\(^7\)

In the last couple of years, published studies have reviewed these new high-sensitivity troponins in cardiac diseases (e.g., AMI, heart failure, decompensated patients, angina).\(^8\)–\(^12\) Nearly all of them concluded that these new troponins are helpful because they have increased sensitivity and are more useful in the triage of patients and early diagnosis of AMI, yet more data is needed regarding the impact of the new high-sensitivity troponins in the early detection of cardiotoxicity.
In this study, 33 breast cancer patients were scheduled to receive anthracycline and trastuzumab with the goal of verifying if more sensitive ecocardiograms or high-sensitive troponins could predict the development of cardiotoxicity. The investigators found that decreases in longitudinal strains and radial strains and elevation in high-sensitivity troponin at three months were predictive of...
patients who developed cardiotoxicity at six months. They had nine cases of cardiotoxicity: one developed at three months and the other eight were detected at six months. With multivariate analysis, only the changes of at least a 10% decrease in longitudinal strains at three months and the increases in high-sensitivity troponin I at three months remained significantly predictive of the cardiotoxicity development. The investigators also tried to combine these two markers and again had some problems with the positive predictive value and a very high negative predictive value. In particular, there was a 10% decrease in longitudinal strain or elevated high-sensitivity troponin at three months that had a very high negative predictive value of 97%.

An ongoing study at our institute consists of 300 blood samples from 79 patients (55 breast cancer and 24 advanced gynecological malignancy patients) taking adjuvant chemotherapy with a minimum of one sample up to a maximum of 21. Two troponins, Stratus CS and the Ultra Centaur, had cut-offs of 0.07ng/mL and 0.04ng/mL, respectively, and the range of value 0.00-0.76ng/mL and 0.00-0.39ng/mL, respectively. The concordance between the two troponins was quite good—95% of the results were concordant. The vast majority of them were negative with both methods, 18 positive with both methods, and 15 cases which were different. Note that 70%, 11 samples, were positive with the conventional troponin and negative with the high-sensitivity troponin.

Observing the patients now, 75 of 79 patients gave us concordant results and 4 of 79 discrepant results. Of the four discrepant results, three of them were breast cancer patients and one was ovarian cancer. A few of these patients had a decrease in ejection fraction—comparing the baseline value and the end therapy value—then they recovered. Some of these patients were false positive results, which is the problem we have now. We have 99% of patients (99% sensitivity), yet a problem with the positive predictive value.

| Table 3. Scorecard Designations of cTn Assays

<table>
<thead>
<tr>
<th>Acceptance designation</th>
<th>Coefficient of variation (CV) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline acceptable</td>
<td>≤ 10</td>
</tr>
<tr>
<td>Clinically usable</td>
<td>&gt; 10 to ≤ 20</td>
</tr>
<tr>
<td>Not acceptable</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Assay designation</td>
<td>Measurable normal values below the 99th percentile, %</td>
</tr>
<tr>
<td>Level 4 (third generation, hs)</td>
<td>≥ 95</td>
</tr>
<tr>
<td>Level 3 (second generation, hs)</td>
<td>75 to &lt; 95</td>
</tr>
<tr>
<td>Level 2 (first generation, hs)</td>
<td>50 to &lt; 75</td>
</tr>
<tr>
<td>Level 1 (contemporary)</td>
<td>&lt; 50</td>
</tr>
</tbody>
</table>
In conclusion, troponin is an early marker which can predict the development of chemotherapy-induced cardiotoxicity and its severity. Troponin has a very high negative predictive value, yet a slightly lower positive predictive value. The negative predictive value allows us a safe identification of low-risk patients (i.e., those patients who probably need a less intensive and less close monitoring). New high-sensitivity troponin allows for the detection of very small cardiac damage and the studies available in patients with different cardiac disease suggest that this is a real improvement not only from the technical point of view but also from the clinical point of view, yet there are no conclusive data on the impact of these high-sensitivity troponins in the prediction of chemotherapy-induced cardiotoxicity. There is a good correlation between the conventional and high-sensitivity troponin and our preliminary data in a very small group of patients indicate that these high-sensitivity troponins may seem suitable to monitor patients treated with drugs containing monoclonal antibodies.

References
4. OBrien PJ. Cardiac troponin is the most effective translational safety biomarker for myocardial injury in cardiotoxicity. Toxicology. 2008;245(3):206-18.
Point-of-Care Cardiac Biomarker Testing to Guide Cardiac Safety During Oncology Clinical Trials

Daniel J. Lenihan, MD
Professor, Division of Cardiovascular Medicine, Vanderbilt University, Nashville, TN

“Cardiac biomarker point-of-care testing for cardiotoxicity is critical. Point-of-care testing prior to chemotherapy can be done and it can stratify high-risk patients.”
—Daniel J. Lenihan, MD

When trastuzumab first came out, it had a high incidence of cardiac toxicity. There was some consideration at the time that such a drug should be taken off the market. For those of you familiar with the impact of trastuzumab, you know that that would be an absolute tragedy. The case has been made to ensure we have good information, and in the case of trastuzumab we found ways to improve the delivery of that drug and now it is considered quite safe.

The general consensus on detecting cardiac toxicity is that it consists of a baseline ejection fraction (EF) measurement and then a repeat study at some time interval—we don’t really know the time interval because it is going to be drug specific. Now keep in mind that up to half of patients admitted in this country with heart failure actually have a normal EF and their prognosis is not that much different than those that have systolic dysfunction. If heart failure is our concern, the EF is only going to get it right about half the time.

It is important to note symptoms are the mainstay of the diagnosis of heart failure, and currently there are no recommendations for biomarker testing or preventive therapy during chemotherapy to detect or prevent heart failure. We know that biomarkers can be a useful adjunct in the management of heart failure patients, and following symptom development of a patient is not good enough to treat heart failure effectively even if you’re a focused cardiologist. Therefore, a documentable change in a test, such as a biomarker, assists us in the management of these patients.

Here is one study that randomized patients to a biomarker-guided approach versus a clinical management symptom assessment follow up approach.¹ The group that had the biomarker approach had improved cardiovascular outcomes, including admissions for heart failure or death related to heart failure. There have been other studies, yet the outcome is the same—biomarkers can help guide therapy in a heart failure population. If we focus on a population of patients being treated for cancer with a potentially cardiotoxic medication, elevated troponin I levels, both early and late during chemotherapy, then we can better guide our identification of a high-risk patient, improve our treatment of those patients, and actually prevent major cardiac events.²

In terms of myocardial ischemia and infarction, we have a conceptual and experimental paradigm that results in the classic adage that “time is muscle.” If you delay treatment to relieve ischemia, the delay results in the progression of viable tissue to scar tissue to a much greater degree.³ No one questions this principle from an ischemia point of view, yet in terms of
chemotherapy a parallel phenomenon exists—if you wait a period of time before detecting or treating cardiotoxicity, your chance of recovery is much less. So this is a really important principle and it’s one that we definitely understand.

Anthracycline (AC)-induced cardiotoxicity is an established problem and, frequently, it’s going to limit the treatment of cancer. The severity of myocardial damage is dependent on a host of factors and there are monitoring techniques (i.e., MUGA or echocardiogram) that have major

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### Table 1. Pilot Study Demographics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>109</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male/Female)</td>
<td>48/52</td>
</tr>
<tr>
<td>Age (years ± std dev)</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>Cancer Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>10</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>55</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>32</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>10</td>
</tr>
<tr>
<td>Prior Myocardial Infarction</td>
<td>4</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>14</td>
</tr>
<tr>
<td>Family History of Early Heart Disease</td>
<td>20</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>32</td>
</tr>
<tr>
<td>Obesity</td>
<td>35</td>
</tr>
<tr>
<td>Smoking</td>
<td>11</td>
</tr>
<tr>
<td>Cardiac Medications</td>
<td></td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>22</td>
</tr>
<tr>
<td>ACE Inhibitor</td>
<td>17</td>
</tr>
<tr>
<td>ARB</td>
<td>13</td>
</tr>
<tr>
<td>Statins</td>
<td>23</td>
</tr>
<tr>
<td>Aspirin</td>
<td>10</td>
</tr>
<tr>
<td>Antplatelets</td>
<td>6</td>
</tr>
</tbody>
</table>

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### Table 2. BNP Toxicity in Patients Receiving Anthracyclines

<table>
<thead>
<tr>
<th>Patient</th>
<th>BNP Value (pg/mL)</th>
<th>Time to Event (min)*</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>215</td>
<td>244</td>
<td>Decreased LVEF/ Symptomatic Arrhythmias</td>
</tr>
<tr>
<td>2</td>
<td>322</td>
<td>2</td>
<td>ACS</td>
</tr>
<tr>
<td>3</td>
<td>279</td>
<td>13</td>
<td>Symptomatic Arrhythmia</td>
</tr>
<tr>
<td>4</td>
<td>303</td>
<td>215</td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td>5</td>
<td>306</td>
<td>25</td>
<td>Symptomatic Arrhythmia</td>
</tr>
<tr>
<td>6</td>
<td>986</td>
<td>0</td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td>7</td>
<td>273</td>
<td>19</td>
<td>ACS</td>
</tr>
<tr>
<td>8</td>
<td>353</td>
<td>33</td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td>9</td>
<td>241</td>
<td>305</td>
<td>Symptomatic HF</td>
</tr>
<tr>
<td>10</td>
<td>155</td>
<td>0</td>
<td>Symptomatic Arrhythmia</td>
</tr>
<tr>
<td>11</td>
<td>264</td>
<td>3</td>
<td>Symptomatic HF</td>
</tr>
</tbody>
</table>

* Number of days from first BNP > 150 pg/mL, LVEF = left ventricular ejection fraction, ACS = acute coronary syndrome, HF = heart failure
limitations and only detect left ventricular (LV) dysfunction where there is substantial decrease. Now, we may have more options with advanced imaging techniques, such as strain rate, yet with the current standards, LV dysfunction has to be pretty substantial before we really detect it.

We conducted a pilot study a few years back, looking at point-of-care biomarkers immediately before and after each round of AC-based chemotherapy (Table 1). In this pilot data, 11 of the 109 patients developed a symptomatic cardiac event (Table 2). The elevated BNP values were detected prior to the event (either on the day of the event or preceding the event)—you had the potential of identifying a person at very high risk many months before the development of a cardiotoxic event.

When we looked at BNP levels for the detection of cardiac toxicity during AC-based chemotherapy, the only factors that were significantly associated with a cardiac event included older age, history of myocardial infarction, and an elevated BNP. The cutoff established prior to the study for BNP was 200 pg/mL or less as a marker of true cardiotoxicity (Table 3). From our study data, if you had two BNPs that were > 100 pg/mL, then that was a significant marker of cardiotoxicity, yet there were a substantial number of patients that may have had a false positive. If you had one BNP that was > 200 pg/mL, it actually conferred a 44 times greater risk of developing a cardiac event.

The LVEF measurement that suggested cardiotoxicity was either > 15% reduction from baseline to a level above 5% or a 10% reduction in LVEF to below 50%. Only 3 patients that had a cardiac event had the LVEF criteria significantly reduced and 7 of the 11 who had a cardiotoxic event did not have a significant LVEF change.
When we look at the accuracy of each test and the cutoff for predicting cardiac events, one BNP > 100 pg/mL was very sensitive, yet the specificity was not so good (Table 4). Negative predictive value was good, yet the positive predictive value wasn’t optimal. If you look at one BNP > 200 pg/mL, you see the sensitivity and specificity is quite good. Negative predictive value is excellent and the positive predictive value is a little stronger. If you look at the LVEF changes, it’s really not very good and having only a 30% sensitivity is probably not acceptable.

This pilot data was very strong so we operationalized this process—which became the PREDICT Study. As it turns out, there are five studies called PREDICT at Vanderbilt so we have to call this one PREDICT Oncology—yet we have four others. PREDICT Oncology is a multi-center trial through the MD Anderson CCOP system, which is a collection of oncology practices and various academic sites across the country. The study officially opened in January 2011 and the first enrollment was in February.

The inclusion criteria are straightforward—any adult (age 18-85) who is going to start a new course of chemotherapy that includes an AC, and a general life expectancy greater than a year. The exclusion criteria are pretty much based on the fact that, if you have established heart disease (e.g., myocardial infarction or heart failure [HF]) we really think that you need to be aggressively followed and treated by a cardiologist during your chemotherapy. Those that have had HF, LVEF < 50%, or previous unstable angina in the last three months are excluded. Patients receiving concurrent dexrazoxane are also excluded because that may have some effect on the biomarkers, yet I’ve never seen a patient actually get dexrazoxane—it hasn’t been very applicable. If the biomarkers are abnormal at baseline, then we believe you already have identified problems.

A cardiac event is defined as symptomatic cardiac arrhythmia, acute coronary syndrome,
symptomatic heart failure, development of asymptomatic left ventricular dysfunction, or sudden cardiac death. There are prescribed echocardiogram measurements at baseline, at six months, and at 12 months, unless you have a suspicion of a cardiac event at which time a cardiology evaluation is needed. As part of the study, point of care cardiac biomarkers are done immediately before each cycle of chemotherapy (Table 5).

There are 275 patients in the study currently and the goal is 830—with an expected 10% rate of cardiac events in this population, this is how many patients it would take to see a meaningful difference in our measurements. Vanderbilt has 26 patients of these patients right now and four of them have had a cardiac event as summarized below.

First case: 19-year old woman with leukemia, previously treated with adriamycin for six cycles, then received two cycles of mitoxantrone and became hypoxic within 2 days. The clinical evaluation included a troponin of 0.09 ng/mL, a BNP of 1,169 pg/mL, and LVEF at 52%. This patient had pulmonary edema on chest x-ray and clinical findings of heart failure.

Second case: 63-year-old woman with previous leukemia, treated with six cycles of adriamycin-based chemotherapy, who then developed shortness of breath and ultimately atrial fibrillation and hypotension. Prior to developing atrial fibrillation, an echocardiogram showed an LVEF of 48% and her previous LVEF was 56%. Her troponin was 0.05 ng/mL, BNP was 371 pg/mL, and she had pulmonary edema on chest x-ray and physical exam findings consistent with heart failure.
Third case: 61-year-old male, known coronary disease, had a previous bypass, developed aggressive lymphoma, received six cycles of adriamycin-based chemotherapy. On his final visit after six months, he was fatigued but had no paroxysmal nocturnal dyspnea or orthopnea. His echocardiogram at the time showed a LVEF of 45% (was 59% previously). His BNP was 157 pg/mL and troponin was 0.2 ng/mL.

Fourth case: 52-year-old man with no previous history, developed promyelocytic leukemia, was treated with adriamycin-based chemo for one cycle, developed neutropenia, then fatigue and shortness of breath. His LVEF on echocardiogram was 47% (was 54%). His BNP was 1,300 pg/mL and troponin was 0.08 ng/mL.

Only one of these four cases of documented heart failure actually had a significant LVEF change that would have met our criteria for cardiac toxicity. All of them had abnormal biomarkers and, in some cases, the biomarkers preceded the event. If this is a window into what we would see from all of the institutions involved, then hopefully it will confirm that we can use a point-of-care device to guide our cardiac safety assessments during an oncology treatment trial—which is a very clinically relevant strategy because most of these sites are clinical practices that are involved in this study. We want to identify the problem early via biomarkers and initiate cardioprotective treatment with ACE inhibitors or beta blockers. Early identification and protective treatment really could make a difference in terms of either prevention of the problem or rapid improvement and, ultimately, that would allow the patient to have more complete cancer therapy.

Cardiac biomarker point-of-care testing for cardiotoxicity is critical. Point-of-care testing prior to chemotherapy can be done and it can stratify high-risk patients. Echocardiogram imaging is clearly important but may not detect small changes and is not frequently feasible due to the expense of repeat testing. Future strategies will encompass identifying high-risk patients and theoretically utilizing direct preventative therapy.

References
Future of Research in CardiOncology: FDA Perspective
Gideon M. Blumenthal, MD
Medical Officer, Division of Oncology Products 1, Office of Hematology Oncology Products/CDER/FDA, Bethesda, MD

“Within the FDA, we are developing a knowledge management database to catalog key design features in early oncology studies to learn about what features enable successful and unsuccessful drug development, and also to pick up on preliminary safety and pharmacodynamics signals in early studies.”
—Gideon M. Blumenthal, MD

Let’s begin by stating some general observations about oncology drug development. In oncology, there is a much greater risk tolerance in treating patients with advanced cancer and other therapeutic areas. Preclinical or early-phase toxicity signals in oncology may halt development if seen in other therapeutic areas. Novel molecularly targeted therapies may have unanticipated on- or off-target effects. These targeted drugs are likely perturbing pathways critical to cardiac function and survival. There are hundreds of targeted agents in development being tested in a variety of malignancies and combinations. Finally, these combinations of targeted agents will likely increase the risk of cardiotoxicity.

So, the landscape of oncology drug development has changed. In the past, we used to look at the cell cycle and develop cytotoxic chemotherapy to target DNA damage in the assays to induce mitotic arrest. Today, more and more drugs are being developed that target proteins, signaling

Table 1. Tyrosine Kinase Inhibitors Approved in the United States

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Target(s)</th>
<th>Indication(s)</th>
<th>CV toxicity (per label)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib</td>
<td>2001</td>
<td>ABL, PDGFR (α/β), KIT</td>
<td>CML, GIST, B-ALL, CMMML, CEL</td>
<td>CHF, LVEF decline, CM, arrhythmia, cardiac death</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2004</td>
<td>EGFR</td>
<td>NSCLC, pancreatic</td>
<td>MI ischemia</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>2005</td>
<td>BRAF, VEGFRs, PDGFR (α/β), FLT3, KIT</td>
<td>RCC, HCC</td>
<td>Cardiac ischemia, HTN</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>2006</td>
<td>BRAF, VEGFR2, PDGFR(α), csf1R, FLT3, KIT</td>
<td>RCC, GIST, PNET</td>
<td>LVEF decline, QT prolongation, HTN</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>2006</td>
<td>ABL, PDGFR, KIT, SRC</td>
<td>CML</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>2007</td>
<td>ABL, KIT, PDGFR</td>
<td>CML</td>
<td>QT prolongation</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>2007</td>
<td>EGFR, HER2</td>
<td>HER2+ breast cancer</td>
<td>LVEF decline, QT prolongation</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>2009</td>
<td>VEGFR, PDGFR, KIT</td>
<td>RCC</td>
<td>QT prolongation, torsades, MI, HTN</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>2010</td>
<td>VEGFR, EGFR</td>
<td>Medullary Thyroid</td>
<td>QT prolongation, torsades, sudden death, ischemia, heart failure</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>2011</td>
<td>BRAF</td>
<td>BRAF + Melanoma</td>
<td>QT prolongation, MI, Aib</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>2011</td>
<td>ALK, MET</td>
<td>ALK+ NSCLC</td>
<td>QT prolongation</td>
</tr>
</tbody>
</table>
transduction pathways that are critical to cancer cell survival and increasingly we may see drugs or a combination of drugs that target multiple pathways to circumvent cancer cell resistance. Many, if not all, of the tyrosine kinase inhibitors have been significant advances in the field of oncology (Table 1). All of them carry cardiovascular risks, which are reflected in the label.

There are multiple challenges in assessing cardiotoxicity in early oncology drug development. Patients with advanced cancer enrolled on early clinical trials are often really very sick, malnourished, cachectic with declining performance status with fatigue and dyspnea. As a clinician, reviewer, and an investigator, it can be difficult to tease out what’s going on. Is this a drug-induced toxicity? Are the signs and symptoms from the underlying malignancy or is there something else going on? In addition, many patients have comorbid conditions. At the NCI Thoracic Oncology Clinic, we see a lot of lung cancer patients who have a variety of comorbid conditions, including coronary artery disease, COPD, and they’re on a host of concomitant supportive medications.

On the flip side, however, high-risk patients are generally excluded from clinical trials. So, data that we generate may not mimic the real world. In addition, refractory metastatic patients are on drugs for short periods of time and it may not reflect long-term cardiac risks or risks in earlier settings, such as the adjuvant setting. As we’ve learned, current methods often detect cardiac toxicity too late and we don’t have enough data on proper patient selection or proper risk mitigation strategies.

Table 2 is the oncology drug lifecycle from an FDA reviewer’s perspective. In terms of cardiovascular toxicity, we look at histopathology, hERG studies, ECG in non-rodents, and any other

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**Table 2. Oncology Drug Life Cycle from an FDA Perspective**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-clinical toxicity</strong></td>
<td>histopathology (necropsy), hERG, ECG (non-rodents), KO mice, tissue cross-reactivity (biologics), troponins</td>
</tr>
<tr>
<td><strong>First in human</strong></td>
<td>Phase 1a in advanced cancer: dose escalation, cardiac inclusion/exclusion criteria; monitoring: vital signs, PhEx, LVEF, ECG, serum biomarkers? (troponins, BNP), dose modification/delay/rechallenge</td>
</tr>
<tr>
<td></td>
<td>Phase 1b (combination)</td>
</tr>
<tr>
<td></td>
<td>Phase 2a/2b</td>
</tr>
<tr>
<td></td>
<td>Phase 3a/3b: DSMB structure; cardiac monitoring: LVEF, ECG, cardiac safety endpoints, stopping rules, long-term f/u</td>
</tr>
<tr>
<td></td>
<td>NDA</td>
</tr>
<tr>
<td></td>
<td>Phase 4, post-marketing surveillance, novel indications: earlier disease settings, adjuvant, novel combinations</td>
</tr>
</tbody>
</table>
data, such as knockout mice data for biologics, tissue cross-reactivity and so forth. Moving onto the first in human studies, we focus on the dose escalation strategy, the eligibility criteria, cardiac monitoring, as well as dose modification, delay, and rechallenge guidelines. If there’s a signal of cardiovascular toxicity, the agency may require additional safety pharmacology studies and a human QT study, which may differ from the thorough QT study in other disciplines. If there’s a cardiac signal in phase 3, we look carefully at the data safety monitoring board structure, the cardiac monitoring in place, cardiac safety endpoints, stopping rules, and long-term follow up. Then once the drug is approved, we may ask for phase 4, post-marketing studies, post-marketing surveillance and, typically, the drug is tested in novel indications or in earlier disease settings or with new combinations.

In conclusion, allow me to highlight some potential areas of opportunity. One, genetic markers of cardiac risk.\textsuperscript{1,2} The agency dispersed draft guidance in February 2011 about clinical pharmacogenetics in premarketing evaluation and early-phase clinical studies. We recommend, yet don’t require, prospective DNA sample collection in early- and late-phase clinical studies. This could be very valuable to sponsors, who in the course of their development program, witness a cardiotoxicity signal. They could go back and query the DNA to see if there might be a germ-line polymorphism associated with this risk. Two, other areas of opportunity include improved biomarkers. One could argue that perhaps troponin and BNP, at least clinically, are already ready for prime time. However, they haven’t been studied as extensively as a drug development tool. Three, other biomarkers could be ECG, novel imaging modalities and CDER Biomarker Qualification process, which qualifies a given biomarker within a specific context of use to aid in drug development. There are a number of biomarkers that are currently in the process of being qualified within CDER and one has already been qualified—a preclinical assay of renal injury. Finally, I wanted to highlight one of the efforts being done in our group. Within the FDA, we are developing a knowledge management database to catalog key design features in early oncology studies to learn about what features enable successful and unsuccessful drug development, and also to pick up on preliminary safety and pharmacodynamics signals in early studies. This could be valuable date for FDA reviewers regarding cardiac signals in novel molecularly targeted therapies or combinations.

References
Early Phase Trials in Oncology: Any Concern for Cardiovascular Toxicity?

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“Accurate publication of data is a must and the lack of standardization of screening and monitoring of patients enrolled in phase 1 clinical trials must be addressed.

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—Apostolia M. Tsimberidou, MD, PhD

To design and conduct successful phase 1 clinical trials with investigational agents, we need to consider the following: clinical data of investigational agents; serious factors for cardiovascular disease; and patient eligibility criteria regarding heart function tailored to patient history and risk factors of heart disease. Monitoring patients for cardiovascular toxicity and prompt management of cardiovascular complications is also important. The cancer therapies associated with cardiotoxicity include VEGF therapies and vascular disrupting agents. I will show you some examples of what we have experienced in the phase 1 program at MD Anderson.

The effects of VEGF therapies in tumor and normal tissues vary.1 For example, lung cancer treated with bevacizumab causes inhibition of tumor growth and cavitation; in hepatocellular carcinoma, sorafenib causes tumor necrosis; in renal cell carcinoma, sunitinib causes tumor cell necrosis; and in colorectal cancer, bevacizumab decreases the rate of tumor growth. In normal tissues, the same drugs cause hypertensive remodeling and cardiomyopathy, particularly sunitinib; in micro-circulation, they cause endothelial dysfunction and vasoconstriction; in kidneys, we see proteinuria and hypertensive nephropathy.

The rate of hypertension was predicted in phase 1 clinical trials, for example, for bevacizumab, about 9% of phase 1 clinical trials showed that there was grade 3/4 hypertension—this was reproducible in both phase 2 and phase 3 clinical trials. Similarly, with sunitinib and sorafenib, the rate of grade 3/4 hypertension was about 7%. Grade 3/4 left ventricular systolic dysfunction was noted in only 0.3% of patients treated with bevacizumab in any phase clinical trials and 1.4% with sunitinib (3.6% phase 1 clinical trials). Sorafenib is less associated with grade 3/4 left ventricular systolic dysfunction.

Thromboembolic complications are more frequent with bevacizumab and less frequent with sunitinib and sorafenib. About 10% of patients treated with bevacizumab had evidence of thromboembolic events, particularly patients with lung cancer. One of the things we do in clinical practice is call the radiologists and ask for the association or the proximity of the tumor to major arteries to avoid the use of VEGF therapies in these patients in order to prevent major hemorrhagic episodes. Sunitinib is less associated with thromboembolic events and sorafenib is about 4%.
Another group, the vascular-disrupting agents, have been investigated in the last three years for other kinds of therapies. Their mechanism of action includes microtubule depolymerization—these drugs can destroy the endothelial monolayer, resulting in extravasation of intravascular macromolecules which results in cessation of tumor blood flow and tumor hypoxia. The end result is tumor necrosis and all these events are associated with robust reactive angiogenesis and tumor regrowth on the periphery.

Some would expect these results to happen not only in tumor cells, but also in normal tissues which brings us to the concern of cardiotoxicity. The majority of these drugs have never reached the point of phase 3 or close to approval clinical trials because of high risk of cardiotoxicity.

We conducted a clinical trial with Azixa\(^{(R)}\) in which two patients developed a myocardial infarction, including one who had history of severe heart disease. Table 1 shows why we should be extremely careful using novel therapies, including VEGF and vascular-disrupting agents, for the treatment of cancer. In my opinion, patients with high risk factors for cardiovascular disease should be excluded from these phase 1 clinical trials. During the last four years, about 1,109 patients seen in the phase 1 program had an echocardiogram and approximately 11% of these patients had an ejection fraction (EF) < 50%. Interestingly, there was no difference in survival by EF. When the cutoff of EF 40% was used, there was no difference in survival and about 3% of patients had an EF < 40%. The data is currently being analyzed and we are looking at other risk factors associated with heart failure as well as treatments that these patients have received.

The role of ß2 adrenergic stimulation is important for cancer and heart function. There are
preliminary data in vivo published from MD Anderson in which animal models showed that β2 adrenergic stimulation leads to greater tumor burden and more invasive tumor growth. Therefore, beta blockers are thought to prolong survival by decreasing tumor growth and metastases and having a beneficial effect on the heart. It would be interesting to run clinical trials, including beta blockers and look prospectively at the role of beta blockers in cancer progression and patient survival.

Based on clinical practice, some of the challenges we face in management of cardiovascular complications of patients enrolled in phase 1 clinical trials are the use of the clinical data for tailoring study design. The FDA is implementing new rules to maximize the use of the clinical data in the design of phase 1 clinical trials and it’s also important to refine eligibility criteria in order to prevent cardiotoxicity and death due to cardiotoxicity, particularly with novel agents. Selection of screening tests is also a challenge and there is a lot of debate about which is the optimal screening test. These data need to be collected and tested in phase 1 of clinical trials and beyond. Monitoring for cardiotoxicity is also a challenge, particularly for first-in-human agents. Accurate publication of data is a must and the lack of standardization of screening and monitoring of patients enrolled in phase 1 clinical trials must be addressed. We need to develop models to predict risk and exclude patients with high risk from phase 1 clinical trials with novel investigational agents. How can we do that?

At MD Anderson, we have about 120 phase 1 clinical trials; 31% are first-in-human, 26% phase 1 not first-in-human. Combination of experimental and commercial drugs are 11% and there are commercial new routes, such as hepatic artery infusion or intraperitoneal chemotherapy of different agents. Of the trials, 5% are a combination of two or more experimental drugs. During the last four years, we have focused on performing biopsies or using archival biopsies to identify molecular aberrations driving tumor progression and metastases according to published data. Of the 1,144 patients, about 40% were found to have a molecular aberration that is targetable. Since we see a number of different tumor types, we had the opportunity to look at the proportion of these molecular aberrations per tumor type. 73% of patients with melanoma had a molecular aberration; 56% of patients with thyroid carcinoma; about 50% of those with colorectal cancer; and 43% of those with endometrial cancer. Sarcoma and renal cancer had very few molecular aberrations.

Whenever possible, we tried to target the molecular aberrations with a novel agent that is known to inhibit the function of the molecular aberration. If there is a decrease below 30%, then the patient has a partial response. If the decrease is 100% in tumor measurements compared to baseline, then the patient has a complete remission. If the change in tumor size is an increase by greater or equal to 20%, then this patient has progressive disease. Any other response is considered stable by the standard criteria. Overall, there was a 50% benefit in patients with advanced cancer seen in our program when we used the personalized approach versus 15% using the standard approach.

This response translated into improvement in time to treatment failure. The median time to treatment failure was 5.2 months in the group treated with the personalized approach versus 2.2 months in the group treated without the personalized approach. The improvement in time to treatment failure was also associated with improvement in survival. There as an improvement of
4.4 months in survival when the personalized approach was used, where the median survival of the group treated with personalized therapy was 13.4 months versus 9 months in the group treated without the personalized approach. Since this was a retrospective analysis with prospective registration but not done in a randomized fashion, we also compared the outcomes of patients with the same patients previous systemic therapy, and we performed the paired analysis. The personalized medicine approach when we treat patients with cancer is better. In the group treated with not much therapy, there was no difference between the treatment patients received in the phase 1 program versus their previous systemic therapy.

Therefore, moving into the personalized medicine era, the short-term goals would be to take into consideration, to individualize patient care, not only for the selection of the cancer therapy but also to monitor closely for cardiotoxicity. We should carefully design prospective clinical trials to assess cardiotoxicity in every phase of clinical trials based on the novelty of the drug and the basic risk factors. We should all work together to refine eligibility criteria and we should raise awareness in academic and community practice about cardiotoxicity of the cancer agents, particularly the VEGF agents, that are very commonly used. We should try to develop algorithms to guide prevention and management of cardiotoxicity and to write the guidelines for ASCO and NCCN in order to optimize patient therapy. We should focus on long-term cardiovascular complications and this is more important since with the user-personalized medicine because the survival of patients with cancer is longer. We should foster the collaboration of cardiologists and oncologists. There were recent discussions at my institution about the importance of having a cardiologist in the same area where we see patients with cancer on a daily basis to avoid late schedule of echocardiograms, monitoring, and cardiology assessment.

The long-term goals should be to use the results prospectively, collect the data from clinical trials to develop a model to predict the risk of cardiotoxicity. It is important to try to identify molecular profiling that predicts for high-risk phenotype for cardiotoxicity and it is probably better to start looking at tissue and then develop a blood test to predict for cardiotoxicity and then use in clinical trials later. It is also important to develop strategies to prevent and to reverse cardiotoxicity and to stratify patients according to cardiovascular risk for participation in every phase clinical trials. Perhaps it is important at this point until new data become available to exclude high-risk patients for cardiovascular disease from phase 1 clinical trials for first in human agents. It is also important to develop and use existing tissue banks to look for cardiovascular complication in patients with cancer versus patients without cancer.

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