Hello and thanks for joining me to learn about the late effects of chemotherapy, a topic I am very passionate about. My name is Diane Hecht and I am a Clinical Pharmacy Specialist at The University of Texas MD Anderson Cancer Center in Houston, Texas. I had the honor of working in the Breast Medical Oncology Clinic here at MD Anderson and the privilege of serving breast cancer patients from all over the world. I hope to provide you with important information that you can use in your practice.

It is my goal for you to achieve the following objectives: first, to compare and contrast long and short-term toxicities of adjuvant chemotherapy currently utilized in the management of early stage breast cancer; to interpret the risks of anthracycline-induced cardiotoxicity; outline the current treatment approach to the management of anthracycline-induced cardiotoxicity in cancer survivors.

To identify proposed mechanisms of post-chemotherapy fatigue in breast cancer; and lastly, to explain the current approach to fertility and birth control in breast cancer survivors after adjuvant breast cancer treatment.

Before I discuss specific short and long-term toxicities it’s important that we recognize that the survival rates for breast cancer patients is now a little over three and a half decades long. This then provides us with a larger number of patients surviving over a longer period of time, and therefore, a larger volume of data to review and analyze. We’ve always focused on short-term toxicities during a treatment phase but now we need to start focusing on long-term toxicities in the post-treatment phase. During treatment we have many good drugs to help control the side effects associated with chemotherapy and biotherapy and the toxicities are moderately well-described because of all the clinical trials. And the symptoms of these toxicities usually resolve within weeks and in some cases months following the completion of treatment. On the other hand, long-term toxicities occur again in the post-treatment phase. These are poorly described because of limited comparative data from clinical trials, and again, this is partly because of struggles with follow-up with patients. It’s harder to get the information and the information that we are capturing is generally directed towards survival, mortality, and less about the quality of life of patients. Needless to say though, this long-term post-treatment phase is very important in a patient’s quality of life, and therefore, we need to start focusing more and more on it, collecting data, analyzing, reviewing, performing analyses, etc.

Improved knowledge of all toxicities can allow for refinement of the adjuvant treatments that we’re giving patients. The more information that we have about what happens after the fact, is information that we can use for the next patient prior to or during the treatment phase. It’s important that we ultimately strive to improve the quality of life for a patient not only short-term but also in the long-term post-treatment phase as well. Again, the goal of early stage breast cancer treatment is curative and so we want them to actually also have a very high quality of life in addition to being alive. I have three principles that I like to use in my practice and clinic and I try very hard to treat these principles. I think one of my major jobs in clinic is to educate patients. And it’s very important that
they understand what the toxicities are that can happen during treatment as well as after treatment. These principles are: Number 1) knowledge is power; Number 2) prevention is key; and Number 3) no unnecessary suffering.

Awareness of the short and long-term toxicities is therefore very important and I would like to briefly go over those with you. In the table on the slide you will see both short-term and long-term toxicities and you'll see some toxicities appearing in both columns. These include fatigue and neuropathy. The other short-term side effects such as alopecia, GI disturbances, myelosuppression, skin disorders, these generally happen because these tissues are affected by the chemotherapy. They have cells that rapidly turn over and so, hence, the hair falling out, the mouth sores, the drop in blood counts, the skin rashes, dry skin, changes in nails. All those things are happening due to the impact of the chemotherapy on that tissue at that time. Long-term effects from chemotherapy and biotherapy, however, are different from short-term. Many of these side effects are a result of a short-term toxicity on a particular tissue or organ. So for instance, many of the long-term toxicities are a result of ovarian failure or ovarian toxicity and these include bone loss, ovarian dysfunction and infertility, sexual dysfunction, and weight gain. I will be talking about many of these toxicities in subsequent slides.

So let’s move on to the --- one of the more common or at least more commonly discussed toxicities and that is cardiac dysfunction. This slide contains a list of the classes of drugs that have known probable or presumed cardiotoxicity, with these drugs utilized in the adjuvant treatment of early stage breast cancer. Most commonly these are the anthracyclines, also include the alkylating agents, anti-metabolites, the taxanes, and then most recently the biotherapy anti-HER2 antibodies. The anthracyclines which are the drugs doxorubicin and epirubicin can cause cardiomyopathy, arrhythmias, and myopericarditis. This can be either a short-term or a long-term effect and I will be discussing more about this in the subsequent slides. To briefly discuss the others, the next group, the alkylating agents, of which the most common drug utilized in breast cancer is cyclophosphamide. This drug in high doses can cause heart block, tachyarrhythmias, congestive heart failure, and hemorrhagic myopericarditis. Again, this is much less common with methotrexate and again more likely to occur with very high doses. The next group are the taxanes. These drugs can cause bradycardia, AV block, atrial and ventricular arrhythmias, congestive heart failure, and myocardial ischemia. What’s important to know about these groups of drugs is that these side effects were mainly seen in the early clinical trials of these drugs which and at that --- at the time was paclitaxel. These side effects were observed in patients that were experiencing hypersensitivity reactions. Both docetaxel and paclitaxel are
formulated with an excipient that many patients have a hypersensitivity reaction to. So many of these cardiac disturbances or dysfunctions were also occurring at the same time as the hypersensitivity reaction. So it’s kind of hard to determine whether or not it was the hypersensitivity reaction, and more than likely the excipient, such as Cremophor® or Tween® 80 in the case of docetaxel rather than the compound itself, the paclitaxel or the docetaxel. Nonetheless, patients were carefully observed, the infusions of these medications were given over longer periods of time, and there was a lot of screening done to make sure that patients with history of heart disease of any type were either not included in the clinical trials and then, thereafter, watched very carefully. Today we rarely see issues associated with this. The last group that I’d like to discuss, as I said earlier, the --- the newest class of treatment in breast cancer --- early stage breast cancer are the anti-HER2 antibodies and in breast cancer early stage, we’re talking about pertuzumab or trastuzumab. Trastuzumab, of course, has been out longer and, therefore, we have a lot more data around its use as well as the incidence of cardiomyopathy or cardiac failure. These are actually rare. I will be discussing these more in subsequent slides but suffice it to say it is rare that a patient with clinically --- with a clinical presentation of heart failure comes to clinic having been receiving trastuzumab or pertuzumab.

This slide, before we get into specifics about the anthracyclines, just highlights that long-term effects are mainly involving the anthracyclines, doxorubicin, epirubicin, and cause cardiomyopathy. Effects from the other drugs can occur but it is very rare.

So now discussing effects on the myocardium from the anthracyclines. Let’s take a step back and just talk about some of the pathophysiology first. Myocardial cells are very unique cells and have unique characteristics. They require enormous amounts of energy requirements, and because of that, they are very vulnerable to impairments of ATP production or stress in general. They have a limited ability to regenerate, and therefore, it may diminish the heart’s ability to cope with subsequent stressors. However, there are also huge reserves to compensate so that’s the upside of this. The mechanism of anthracycline-induced cardiotoxicity is quite complex. What we believe is that the major mechanism is thought to be due to oxidative stress and calcium and iron dysregulation. The myocytes undergo apoptosis and necrosis from high concentrations of anthracyclines and this can induce myosart --- sarcomere disruption.

There’s a hypothesis called the multiple-hit hypothesis which describes the presence of preexisting cardiovascular disease risk factors as a strong predictor for the development of therapy-induced cardiovascular injury, and therefore, a greater lifetime risk of developing cardiovascular disease. So again, it’s very important that we identify our patients’ comorbidities and --- and perform a thorough physical exam, review of symptoms, past medical history, etc., prior to starting chemotherapy. These preexisting car --- comorbidities as well as lifestyle choices can increase the risk of chemotherapy or biotherapy-induced cardiotoxicity. Things that you want to screen for include hypertension, diabetes mellitus, hyperlipidemia, hypercholesterolemia, and in addition, a patient’s weight and BMI as well as their activity or inactivity. Compared to age-matched controls previously healthy survivors of cancer develop mo --- more
comorbidities or tended to reduce physical activities once they get cancer. So it’s very important that we as healthcare providers recognize this important fact and remind ourselves to constantly remind the patients to stay as active as they can be during and after their treatment. Lastly, I want to point out that late-onset cardiotoxicity builds on pharmacologic and non-pharmacologic sequential injuries.

So let’s talk about the clinical presentations of anthracycline-associated cardiotoxicities. In terms of the acute phase, what you could possibly see are arrhythmias, sometimes heart failure, and/or myopericarditis syndrome. This acute cardiotoxicity would --- would occur during an infusion or within days of an infusion. This is not dose-dependent unlike the long-term cardiotoxicity and is usually reversible. This is uncommon and occurs in less than 1% of patients.

Chronic anthracycline-associated cardiotoxicity, on the other hand, can cause cardiomyopathy, asymptomatic or symptomatic progressive decreases in left ventricular ejection fraction often resulting in congestive heart failure. This can occur early within one year of treatment or have a late onset which would occur after one year post-treatment. This cardiotoxicity is dose-dependent and it is commonly irreversible. So it’s very important that we understand this cardiotoxicity.

So chronic heart failure is the usual clinical presentation of chronic cardiotoxicity from anthracyclines. It may represent a consequence of the heart being unable or no longer able to compensate for that initial damage that occurred around the time of chemotherapy. Just because a patient’s left ventricular ejection fraction is stable does not necessarily mean that they do not have cardiotoxicity. So it should not be taken as evidence of lack of cardiotoxicity, because as I mentioned earlier, the heart has huge reserve --- reserves --- [excuse me] --- to compensate. Clear symptoms of chronic heart failure become evident only relatively late in the development of the disease. So it’s very important that we pay attention to subtle clinical signs and symptoms that patients may be experiencing. Examples include tachycardia that persists after minimal exercise or minor loss of exercise capacity and/or arresting tachycardia. You will also want to monitor systolic and diastolic cardiac function on an ongoing basis.

Now let’s talk about the incidence of anthracycline-induced chronic cardiotoxicity. This reaches approximately 5% with cumulative doses of 400 mg/m² of doxorubicin and 920 mg/m² of epirubicin. It’s also important to recognize that the incidence rate is closer to the 10% in patients over the age of 65. It’s also important to recognize that the curve for the incidence of heart failure exponentially increases with doses of doxorubicin exceeding 500 mg/m² and doses of 950 mg/m² of epirubicin.

The Early Breast Cancer Trialists’ Collaborative Group in their 2000 overview analysis reviewed the cardiotoxicity with anthracyclines and anthracycline-based trials. So the aggregate of all anthracycline-based trials was a little over 11,500 patients and they compared this to trials with no chemotherapy or with chemotherapy without an anthracycline, such as CMF chemotherapy, and this was a --- also a little over 11,800 patients. The differences in vascular mortality are not significant. They indicate a
hazard of only a few per thousand per decade in these trials. It could be that with longer term followup or different anthracycline-based regimens that this --- that this information changes. So it is important that we keep an eye on this and we continue to follow the Early Breast Cancer Trialists meta-analyses as we continue over the --- the --- the next subsequent years.

Now I’d like to talk about the risk factors for anthracycline-induced cardiotoxicity because again, prevention is key and knowledge is power. So it is very important that clinicians understand the risk factors and do what they can to --- to --- to utilize this information in their practice and protect patients. Again as I alluded to in the previous slides, cumulative dose of doxorubicin and epirubicin is very important. So I recommend that you just --- as you’re documenting in your notes the patient’s therapy, that you keep a running tab of what their cumulative dose of that anthracycline is. That way, as you’re going along, you’ll make it easier and you can always go back and take a look at it especially should something happen in the future and you want to go back and look and see how much cumulative dose of an anthracycline a patient received. Next, the --- the type of administration is also very important. We know that bolus administration of anthracyclines is more detrimental to the heart than a continuous infusion or a longer infusion than that bolus administration over 15 minutes. Likewise, preexisting cardiac disease and hypertension are also --- well-known risk factors for anthracycline-induced cardiotoxicity. Again, it’s very important that you know what these are prior to you starting the patient on chemotherapy, especially anthracycline-containing chemotherapy. Next, a patient --- older age, so patients over 65 to 70 years is another well-known risk factor for anthracycline-induced cardiotoxicity that we need to be very thoughtful about. That’s not to say that a patient that age or older cannot receive an anthracycline. It just means that you have to do the appropriate screening and assessment upfront. It may be that you want to get the patient’s ejection fraction prior to administration of an anthracycline. Next, is prior mediastinal or radiation for --- for other reasons. It may be that, in my experience, I’ve had patients who are Hodgkin’s or non-Hodgkin’s lymphoma survivors who have experienced mediastinal irradiation as a treatment for that previous disease and they are at risk for anthracycline-induced cardiotoxicity. And then lastly, female gender was found to be an independent risk factor.

Again, prevention is key. What you want to do is to limit the total cumulative lifetime dose in your patients. Okay? This is especially important in patients’ age over 65 and those with a relatively low baseline left ventricular ejection fraction which is approximately 50-55%. Again, other options for you, would be to administer an anthracycline by a prolonged infusion such as a 48 or 72-hour infusion rather than that 15-minute bolus. You could also use novel delivery symptom --- systems --- [excuse me] --- such as liposomal formulations. And then lastly, there is the cardioprotective agent dexrazoxane, which we know prevents free radical generation by chelating intracellular iron. However, I should caution you that the use of dez --- dexrazoxane is not generally suggested in early stage breast cancer patients.
Now let’s talk about treatment of risk factors associated for cardiovascular disease. And so you can look to the American Heart Association guidelines for prevention of cardiovascular disease in women. You want to maintain blood pressure control. This is very important in addition to keeping an eye on their --- their lipids and their cholesterol and having them maintain their lipid-lowering therapies such as HMG-CoA reductase inhibitors. You want diabetics to maintain glycemic control. And you want to continue to reiterate to them that they should be adhering to healthy behaviors such as abstaining from smoking, doing as much physical activity as possible at recommended levels and maintaining a healthy diet. Early detection of chronic vas --- [excuse me] --- cardiovascular disease is also very important.

In terms of monitoring for cardiotoxicity from anthracyclines there are no established guidelines for the optimal intervals and the total duration of monitoring or by what method for that matter. We do have information from the SEER database and it showed that congestive heart failure rates continued to increase up to 10 years post-treatment in women age over 65 who receive anthracyclines. So taking that information, annual monitoring for a minimum of five years should occur for young patients in the absence of progressive left ventricular ejection fraction decline and 10 years --- a minimum of 10 years for elderly and/or patients with progressive ejection fraction declines. Systolic function can be measured through evaluation of --- of MUGA or by echocardiography.

Treatment of anthracycline-induced cardiotoxicity mainly follows the American College of Cardiology or the American Heart Association heart failure guidelines. There are not specific evidence-based recommendations revolving around these cancer patients so we have to look to the AHA and the ACC guidelines. Stage A should focus on risk factor reduction for prevention of remodeling. Again, you want to control hypertension, diabetes, and hyperlipidemia. So having your patients maintain their appointments and their relationship with their primary care physicians is going to be very important. And it’s important that we stress to our patients that they have to maintain that relationship and keep those appointin --- appointments --- [excuse me] --- as much as possible. For Stage B, C, and D, treatment goals are to improve survival, slow the disease progression, and alleviate a patient’s symptoms. So in this situation in these stages you want to combine angiotensin-converting enzyme or ACE inhibitors or an ARB which is an angiotensin II receptor blocker and a beta-blocker unless it’s contraindicated.

A prospective study at the European Institute of Oncology, University of Milan, was performed in order to evaluate anthracycline-induced cardiomyopathy and its response to heart failure therapy. Patients included in this study had a left ventricular ejection fraction of less than or equal to 45%. The primary endpoint of the study was left ventricular ejection fraction response to treatment. Patients were considered responders, partial responders or non-responders according to complete, partial, or no recovery in LVEF, respectively. Responders were defined as those having an ejection fraction that increased up to the normal limit of 50%. Partial responders were defined as those who had an increase in left ventricular ejection fraction of at least 10 absolute points but did not reach the 50% mark. Non-responders were those with an ejection
fraction less than 10 absolute points and an absolute percentage that did not reach 50%. Lastly, a secondary endpoint of this study was occurrence of major adverse cardiac events during the follow-up period.

Study treatment consisted of enalapril 2.5 to 5 mg/day in addition to carvedilol 6.25 mg/day, and lastly, additional pharmacologic treatment as needed per standard of care and these included drugs such as diuretics, anti-coagulants, and anti-arrhythmic drugs.

The table on this slide includes the study results. The first two rows, ejection fraction response and the cumulative cardiac events, represent the primary and secondary endpoints. The columns include the total patients in addition to or followed by the responders, partial responders, and non-responders. There were a total of 201 patients in the study. 42% or 85 of the patients were considered responders, 13% partially responded, and 45% were non-responders. In terms of the cumulative cardiac events there was a lower --- this --- the events were lower in the responder group compared to the partial and non-responders and this was statistically significant. I also want to point out that the percentage of heart failure patients in Class III and IV for all patients was 26%, and that third row includes the percentages for the other groups. So 13% of those 53 patients with New York Heart Association Class III and IV were responders, 18 were partial responders, and 24 were non-responders. Lastly, the median time to heart failure treatment, described in months, was two months for the responders, four for the partial responders, and 17 in the non-responder groups.

The mean follow-up after the start of the heart failure treatment was 36 plus or minus 27 months with a range of 12 to 96. The time to heart failure treatment and the New York Heart Association class were the only predictors of lack of complete ejection fraction recovery. There was an 84% positive predicted value for complete ejection fraction recovery when patients had both timed heart failure treatment less than six months and a Heart Association functional class of I or II.

Therefore, the study authors concluded that early detection and prompt initiation of modern heart failure treatment is critically important to prevent heart failure and to treat patients in a phase in which the disease is potentially reversible.

So now I’d like to shift a little bit and talk about the cardiotoxicity of non-chemotherapy agents, and in this case, specifically, the human epidermal growth factor receptor-2-targeted agents trastuzumab and pertuzumab, otherwise known as the anti-HER2 monoclonal antibodies. Cardiotoxicity with these agents includes symptomatic and asymptomatic reductions in left ventricular ejection fraction. These are actually --- the asymptomatic form is actually the most common presentation. It can also, however, include congestive heart failure, cardiomyopathy, arrhythmias as well as hypertension.

The pathophysiology of cardiotoxicity from these biotherapy agents is not fully understood but it’s likely attributed to blocking the HER2 signaling in cardiac myocytes. We do know now that --- that HER2 signaling, those receptors and proteins that signal
transduction, occurs in cardiac myocytes as well. So it is likely that inhibition also occurs on those cardiac myocytes. *In vivo* and *in vitro* studies have identified importance of epidermal growth factor signaling in normal heart function. This is a different mechanism and is also a different clinical course, in contrast to the anthracycline-induced cardiotoxicity. Lack of anthracycline-typical cardiac structural changes and myocyte destruction is what you see with these anti-HER2 monoclonal antibodies. There is potential for recovery. That’s the good news. Most of the time the cardiotoxicity that is seen with these drugs is reversible upon treatment discontinuation. And honestly, most patients are rechallenged after a drop in ejection fraction has occurred and tolerate it just fine. So the good news, again, is that the cardiotoxicity with these drugs is potentially reversible but it is important that we identify it, we potentially halt treatment, we have our patients seen by a cardiologist, and we start standard treatment for heart failure quickly as well.

Again, the incidence of anti-HER2 monoclonal antibody-induced cardiotoxicity varies according to patient-related factors like the anthracycline. So patients with preexisting heart disease, those of an older age, in addition to the setting, adjuvant or early stage versus a metastatic setting, as well as concurrent therapies, all impact the incidence of trastuzumab or pertuzumab-induced cardiotoxicity.

In 2012, Moja et al., published a systematic review from the Cochrane database. And this meta-analysis of randomized controlled clinical trials compared the efficacy and safety of trastuzumab alone or in combination with chemotherapy or no treatment or standard chemotherapy alone in HER2-positive early stage disease patients. There were 6 adjuvant and 2 neoadjuvant trials included in this meta-analysis and nearly 12,000 patients. The median followup ranged from 18 months to 65 months. The safety results are included in the table on this slide. The traz --- tum --- tuzumab-based treatment regimens, the total patients and --- were approximately 5,500, the non-tuz --- trastuzumab-based therapy was approximately 4,800. So looking at the difference, the relative risk between those two groups was five and it was a significant p value. Reduction in left ventricular ejection fraction, again for the trastuzumab based therapy, was 11.2% and in the non-trastuzumab-based therapies it was 5.6% for relative risk of 1.83 which was not significant.

So trastuzumab significantly increases the risk of heart failure and left ventricular ejection fraction decline. It does, however, improve the overall survival and disease-free survival in women with HER2-positive early stage and locally advanced breast cancer. So again, it’s risk versus benefit but the improvement in overall survival and disease-free survival is quite significant and so, even with the increased risk of heart failure and ejection fraction declines, for most patients the benefit outweighs the risk. Now considerations included the --- in --- in this particular meta-analysis are that patients in the trials were relatively young. All trials required normal heart function for inclusion. Five trials required specific left ventricular ejection fractions prior to starting trastuzumab therapy. So therefore, the risk of cardiotoxicity may be greater in the general population.
Risk factors of trastuzumab-related cardiotoxicity associated with a higher likelihood include: previous or concurrent anthracycline use, age greater than 50 years, preexisting cardiac dysfunction or decreased left ventricular ejection fraction, a high body mass index, and history of antihypertensive therapy.

So, moving on to cardiotoxicity of not only trastuzumab but looking at combined HER2-targeted therapy which would be trastuzumab in combination with pertuzumab, there were two randomized multicenter Phase II studies which captured this data, the NeoSphere trial and the TRYPHAENA trial. NeoSphere was a combination of pertuzumab and trastuzumab, or both with docetaxel, and a combination of pertuzumab and trastuzumab without chemotherapy. There were 417 patients in this NeoSphere trial and these patients had locally advanced inflammatory or early stage HER2-positive breast cancer. The TRYPHAENA trial was pertuzumab plus trastuzumab in combination with standard anthracycline-containing and anthracycline-free chemotherapy regimens and this study had approximately 225 patients.

Adding pertuzumab to trastuzumab when combined with chemotherapy was found to not increase the rate of cardiac dysfunction. We do, however, need long-term follow-up data after exposure to that dual HER2-targeted therapy in the neoadjuvant setting. It’s still too early for us to know for sure, but at this point the results look promising in that it does not increase ---[excuse me] --- the use of combined HER2-targeted therapy does not increase the rate of cardiac dysfunction. So that’s great news.

In terms of monitoring your HER2-targeted therapy, again, baseline evaluation is critical. If we don’t have the baseline, we don’t know what to make of an ejection fraction that happens later on, especially if it drops. Many drugs, in terms of dose reductions, are based on the percentage of drop that can occur. If we don’t know what the baseline number is, we won’t know what kind of a drop that patient incurred. So history and physical exam is necessary at baseline evaluation in addition to measuring a patient’s left ventricular ejection fraction by either echocardiogram or a radionuclide angiography or MUGA.

Subsequent monitoring should occur on an ongoing basis. The optimal surveillance is not defined but we do have guidelines. And what we do generally use is what is proposed by the manufacturer and included in the package insert. So every three months during trastuzumab or pertuzumab therapy your patient should have additional measurement of the ejection fraction. In addition, it sh --- this should also occur four weeks after interruption of anti-HER2-targeted therapy, and then every six months for at least two years following discontinuation of therapy. And this is where --- this last bullet point I think, is very important because this is where it tends to drop off. Many clinics are very good about remembering to not only get that baseline ejection fraction and to monitor it on an every-three-month basis for that first year, but they tend to forget about the every six months for two years following the discontinuation of therapy. And so that’s something that we should try and remember and do a better job of.
So let’s turn now to cognitive dysfunction. Cognitive dysfunction is a growing concern pertinent to long-term effects of adjuvant chemotherapy. And I think this is one where you will hear a lot of patients bring it up and talk to you about it, I think mainly out of concern. A lot of patients want to maintain their present lifestyles, go back to their usual jobs, and they don’t want to have to deal with a different cognitive function than what they had had prior to chemotherapy. We do know that approximately 15 to anywhere upward of 50% of breast cancer patients receiving adjuvant chemotherapy report some level of dysfunction in published studies. Unfortunately, there is a lack of appropriately selected control patients and baseline assessments, so it’s hard to make out what to do with that information. These studies also have utilized different neuropsychological tests and they have varied definitions of cognitive dysfunction. So it’s going to be important for us as a medical community to come to an agreement as to what those baseline assessments and ongoing neuropsychological tests should be, as well as to actually continue to execute those and document that information. There have been two meta-analyses published, one in 2005, and the second in 2006, both with similar findings. The evidence for cognitive diff --- decline related to chemotherapy does exist. None re --- reached clinically significant levels. So that’s good news.

A meta-analysis was published by Dr. Jim and colleagues in 2012, of approximately 800 breast cancer survivors treated with standard dose chemotherapy. These patients were greater the --- greater than or equal to six months post-treatment and they underwent a number of neuropsychological tests in eight different cognitive domains listed on this slide for you. Results of patients previously treated with chemotherapy are that they performed significantly worse on tests of verbal ability than individuals without cancer. In addition, patients treated with chemotherapy performed significantly worse on tests of visuospatial ability than patients treated without chemotherapy. There was also a trend toward worse performance in executive functioning.

So the authors concluded that, on average, patients can expect slight, focused deficits in verbal and visuospatial ability and normal functioning in other domains greater than or equal to six months post-chemotherapy. Patients need education on expectations of cognitive function return. This is very important so that patients can report those cognitive difficulties and that we can then have them evaluated by neuropsychologists, accordingly. We also need to continue efforts on establishment of a core set of neuropsychological tests that are used in clinical trials as well as outside of clinical trials in order to best serve our patients.

The etiology of cognitive dysfunction is not well understood. Existing hypotheses include the following: first, polymorphisms of gene multidrug resistance 1 or MDR1; next, changes in gene which encodes the apolipoprotein E or APOE; and then lastly cytotoxic drugs or their metabolites are able to cross the blood brain barrier and cause cellular toxicity, sequelae of microvascular injury, tissue his --- hypoxia, altered cerebral metabolism, or release of inflammatory cytokines.

So in summary, existing data suggests that cognitive dysfunction occurs, although it’s subtle and mainly involving memory deficits. It is not interfering with ordinary activities
of daily living, thank goodness. We do need prospective, randomized, controlled long-term longitudinal studies though and using validated neuropsychiatric testing. Inclusion of pretreatment baseline studies will also be critical to the design of these clinical trials.

Now moving onto fatigue. So fatigue was one of those side effects that was listed on that previous slide with the table that had short-term and long-term toxicities. I think in the short-term, fatigue is generally a result of the fact that they’re getting chemotherapy, their blood counts are changing, they feel sick, they’re nauseated, there’s a lot of emotions going on, fear, etc. This is different from the fatigue that occurs in a post-treatment phase. Research suggests that approximately 33% of breast cancer survivors report significant fatigue symptoms. It frequently occurs with depression and sleep disturbances which makes sense but it does cause substantial impairment in quality of life.

Therefore, it is important for us to identify the etiology. Basic research in the neurosciences has shown activation of proinflammatory cytokines, such as Interleukin-1 beta, Interleukin-6, tumor necrosis factor α. And these inflammatory mediators have been linked to altered central nervous system activity. Changes in pro-inflammatory cytokines have been found in fatigue, in other fatigue-related disorders. Next, dysregulated cytokine production is also reported during cancer treatment.

Studies have also demonstrated increased serum markers of pro-inflammatory cytokine activity and correlated changes in T-lymphocyte subsets in breast cancer survivors with no evidence of disease and fatigue three to five years after treatment.

Therefore, screening, assessment, and management of fatigue in adult cancer survivors is now becoming important and is becoming reviewed. As you can see on this slide, the American Society of Clinical Oncology has a Guideline Adaptation that was based on the Canadian guideline on fatigue published in 2011. The NCCN® guideline also produced a cancer-related fatigue guideline in 2013 and a survivorship guideline in 2013. They are also attempting to define fatigue. And they have chosen to define it as follows: it’s a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with a patient’s usual functioning. So that’s key. And it is like many of our other definitions of toxicity that our patients experience in terms of the CTCAC — CTCAE — [excuse me] — and that we are looking at impact of that particular toxicity on a patient’s usual function. Screening is important and should be routinely performed and documented using quantitative assessments as clinically indicated but at least annually.

These include history and physical exam. You should perform a fatigue history. You should evaluate their disease status and you want to assess treatable contributing factors: patients’ comorbidities, their medications, abuse of alcohol and any other substances, in addition to reviewing, identifying, discussing the patient’s nutrition, as well as their physical functional status. You also will want to evaluate the patient’s labs,
their CBC with diff, and make sure that their counts are okay, as well as a metabolic panel, and a TSH level.

Management, again, includes education and counseling. One of the things that we can do in fatigue is to treat the contributing factors. So those factors would include things such as depression, anxiety, emotional distress, sleep disturbances, pain, nutritional deficits, anemia, side effects from medications, deconditioning, and other types of comorbidities can definitely contribute to fatigue. And so by tackling all these different contributing factors you may be able to make a fairly significant difference in a patient’s fatigue or at least reporting the patient’s fatigue symptoms. There are no clear standards for interventions but options include physical activity, psychosocial interventions, and also, importantly, mind and body interventions such as yoga or meditation.

So, on the next slide I have more information about intervention options. Again with physical activity you want to initiate and maintain adequate levels of physical activity. This is well-supported in meta-analyses, systematic reviews, and randomized trial evidence. Psychosocial interventions such as cognitive behavioral therapy can reduce fatigue. This is also supported by meta-analyses, systematic reviews, and randomized trial evidence. Psychoeducational and educational therapies may also reduce fatigue and this is supported by systematic reviews and randomized trials. So you see there is good evidence for physical activity and psychosocial interventions to manage fatigue in our cancer patient survivors.

With mind-body interventions, again, there are randomized trials that show improvement in fatigue using yoga as well as acupuncture and something called mindfulness-based approaches. Lastly, the pharmacologic intervention is an option although with limited evidence of effectiveness. So these would be drugs such as psychostimulants, such as methylphenidate rather. These are wakefulness agents and --- that can potentially help them. Supplements are also things that patients really like to focus on, I think, in part because they have access to it. They can access the internet, they can look up information, they can go to a local whole food store and obtain that --- those --- those products. But it is important to recognize that these supplements, such as ginseng and vitamin D, lack consistent evidence of effectiveness and can cause drug interactions. So it’s very important that you educate your patient on all of the things that they are taking, both in the form of drugs as well as in the form of food, drink, alcohol, etc.

So in summary regarding fatigue, it is prevalent in cancer survivors. The cause is multifactorial. It definitely can disrupt a patient’s quality of life. Guidelines and systematic reviews have, therefore, been developed but robust evidence on the management of fatigue is still lacking and still ongoing. So please keep an eye out for more evidence. Non-pharmacologic treatment approaches have demonstrated efficacy. And I definitely urge you to learn about these non-pharmacologic treatment options and suggest them to your patients or refer them to individuals that can help them with these
treatment approaches. Studies --- lastly, studies have failed to find an effective preventative measure.

Now moving onto ovarian dysfunction. Adjuvant chemotherapy frequently results in direct toxicity to the ovary, and of course then this causes premature menopause. If you take a minute to recognize [that] many breast cancer patients are being diagnosed at an earlier age. Historically we thought about our patient population as mainly being menopausal women. That’s not the case anymore. In addition to males having breast cancer, there are many premenopausal patients being diagnosed with breast cancer. These younger women are at high risk of experiencing the ovarian failure. And the degree of damage to the ovary depends on the type of treatment that they receive as well as their age. So in terms of treatment, the alkylating agents such as cyclophosphamide, are generally thought to be --- most commonly cause ovarian failure; second, would be the platinum analogs; and next, would be the anthracycline class. Age over 40 years is also a risk of permanent loss. Okay, and as you can see the range is very broad. It ranges from 10-90%. Again, this is because of the difference in treatment regimens and the age of the patients now undergoing treatment for early stage breast cancer. The degree of damage to the ovary determines whether or not that amenorrhea is temporary or permanent. And thirdly and importantly, there is no therapy that’s been shown to preserve fertility in patients on chemotherapy. We get asked this question many, many times, and unfortunately, we don’t have anything right now that we can give to patients to preserve their fertility. Nonetheless, chemotherapy-induced ovarian failure in premenopausal women, as I mentioned before, leads to a variety of effects on patient health outcomes in the long term. And these include weight gain, bone loss, and potentially infertility.

So let’s first talk about the ovarian failure on weight gain. The mechanism is thought to be multifactor --- factorial --- [excuse me] --- including hormonal changes. The majority of patients in the adjuvant setting experienced gained weight in the range of 2.5 to 6 kilograms. This can be clinically significant and increase a patient’s risk of breast cancer recurrence and mortality. We do have evidence that suggests that weight gain over time, and especially in the survivor population, increases a patient’s risk of recurrence and mortality in addition to re --- increasing a risk of cardiovascular disease as well as diabetes. There is emerging evidence that certain subtypes may also be at greater risk and this actually includes patients with ER-negative or PR-negative estrogen receptor or progesterone receptor-negative cancers. I also would like to point out that the NCCN® panel recommends that patients maintain an active lifestyle and maintain their ideal body weight with a BMI between 20 to 25 for optimal patient health and breast outcomes.

Next, bone loss. Bone loss occurs soon after the initiation of chemotherapy within the first six months. Again, this is more than likely due to the effects on the ovary. It potentially increases the risk of osteoporosis and subsequent bone fractures. What we can do is to attempt to address the modifiable risk factors. You want to recommend regular weight-bearing exercise and maintenance of physical activity. Supplemental calcium and vitamin D is also extremely important. It’s also important to monitor and
continually assess your patient’s bone health over time and you can do this through the use of dexascans on an annual or every other year basis.

Next, moving to fertility and birth control, which is --- which is also a[n] effect from chemotherapy-induced ovarian failure. It’s important to review current approaches to fertility and birth control in breast cancer survivors after the treatment of breast cancer. The majority of women younger than age 35 at the time of treatment resume menses within two years of finishing their treatment. But what’s important to recognize is that resumption of menses does not necessarily correlate with fertility. The absence of menses does not indicate len --- lack of fertility as well. And lastly, limited data exists for continued fertility after chemotherapy. Next, and very importantly, hormone-based birth control is highly discouraged regardless of whether or not a patient’s hormone receptor status is positive or negative. It is very important that patients be counseled on using the barrier method and intrauterine type devices for birth control.

Regarding fertility and birth control, ASCO Guideline Update was published in July of 2013. Providers are encouraged to advise patients on fertility threats as soon as feasible to allow for the widest range of options for fertility preservation. It’s very important that this be addressed upfront prior to the start of treatment. Sperm and embryo cryopreservation as well as oocyte cy --- cryopreservation are considered standard practice and are widely available. For males, sperm cryopreservation or sperm banking is the only established fertility preservation method that is recommended. In females, embryo and oocyte cryopreservation are established fertility preservation methods recommended by ASCO.

So moving away from ovarian-induced failure, let’s talk about peripheral neuropathy in adult cancer survivors. This is another one of those toxicities that appeared on both the short-term and long-term toxicities that can occur in cancer patients. Chemotherapy-induced peripheral neuropathy, unfortunately, is a common adverse effect. It is dose-dependent and it is caused by multiple different types of chemotherapy --- classes of chemotherapy. The neuropathy is symmetric, distal, and generally described as a length-dependent “glove and stocking” distribution. These are predominantly sensory symptoms secondary to sensory axonal damage and this is opposed to the motor symptoms. ASCO clinical practice published a guideline in 2014. And this group was tasked with identifying what are the optimum prevention and treatment approaches in the prevention and management of chemotherapy-induced peripheral neuropathy in adult cancer survivors.

This guideline was published by Dr. Herschman et al., in Journal of Clinical Oncology in 2014. I would encourage you to look at those guidelines. Treatment of existing chemotherapeutic peripheral neuropathy includes a moderate recommendation for the use duloxetine, and this is based on efficacy data from a Phase III randomized, placebo-controlled trial. Duloxetine is an anti-depressant and it --- it is a serotonin norepinephrine reuptake inhibitor or an anti-depressant. It can cause drug interactions, so that is something that you want to be thoughtful about before you would potentially start a patient on this medication. Additionally, other tricyclic antidepressants,
gabapentin and a compounded gel of amitriptyline, baclofen, and ketamine may be offered on data from their utility and other types of peripheral neuropathy such as diabetic neuropathy. In the situation if you have a patient that has limited options, for example, if there are drug interactions or other issues related to toxicity, it may be that you have to try tricyclic antidepressant gabapentin or this compounded gel.

Regarding recommendations for prevention, unfortunately, there are no recommendations, no recommended agents at this point in time. We have no good evidence to suggest. The only thing that you can do is decrease the dose or the duration of the offending chemotherapy. We definitely need further research in this area and this is ongoing now. And I look forward to something happening in the future because this is definitely something that is problematic for patients and can reduce a patient's quality of life.

So I’d like to summarize this presentation with the following thoughts. The potential toxicities of adjuvant chemo and biotherapy can be acute or long-term appearing months to years after treatment. Anthracycline-induced cardiotoxicity is a serious side effect which can exhibit an early or late-onset, with late-onset actually being more common than early. Early detection and prompt initiation of heart failure --- modern heart failure treatment is very important in the management of cancer survivors with anthracycline-induced heart failure. Additionally, use of the HER2-targeted therapies results in small to modest risk of cardiotoxicity exhibited by a drop in left ventricular ejection fraction and less often clinical heart failure.

The incidence, etiology, and management of cognitive dysfunction and fatigue in breast cancer survivors is less well understood but continues to be studied. Next, adjuvant chemotherapy for breast cancer may cause ovarian dysfunction and impair fertility well after treatment completion. Again this is important especially in your patients who were premenopausal at the time of systemic treatment for their early stage disease. Chemotherapy-induced peripheral neuropathy of the sensory type is a common finding in adult cancer survivors also affecting both short and long-term quality of life. Sadly, existing evidence-based options for its treatment or prevention are minimal and further research is needed. This concludes the presentation. I thank you for your participation and welcome your feedback.