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The Latest Medical and Complementary Approaches for Advanced Breast Cancer

Gloria J. Morris, MD, PhD

Steven Rosenzweig, MD

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MODERATOR:

I want to welcome you all to the session on advances in metastatic disease, advanced cancer. My name is Jill Cohen. I live in Seattle, Washington. I was diagnosed originally in 1999, and my cancer recurred in 2002 with extensive metastatic disease, so it's been four years and a couple of months. I am stable and have been stable on aromatase inhibitors. I'm very fortunate. I have 23 sites of bony metastases from the back of my head to my thighs, and yet I walk and talk and sing and dance and have a good time with life in general. It's my pleasure to be here with you today. (Applause)

I would like to introduce Dr. Gloria Morris. She is an assistant professor of medicine in the division of medical oncology at Thomas Jefferson University Hospital [in Philadelphia, Pa.]. She's a graduate of the Medical Scientist Training Program at Medical University of South Carolina in Charleston, with her thesis work in "Chemotherapy: Drug Resistance Mechanisms." She completed her internship and residency training in internal medicine at Jefferson and her fellowship training in medical oncology at Fox Chase Cancer Center. Her special interests include breast cancer therapeutics, bone health in cancer patients – I'm very glad to hear that – treatment of central nervous system metastases and primary brain tumors and translational clinical trials. Dr. Morris? (Applause)

GLORIA J. MORRIS, MD, PhD:

Good morning. Thank you for the invitation to speak to you this morning. My task is to bring you an update on medical advances for advanced breast cancer. I will try to summarize this as much as possible in the next 20 minutes so that we can hear from Dr. Rosenzweig about complementary approaches and hopefully meld this together for you in a good overview and answer your questions afterward.

When we speak about advanced breast cancer, as Jill was mentioning, we lump this into the categories of whether the breast cancer is recurrent, has come back in the same site or has metastasized or gone outside the breast to various sites.

If breast cancer comes back, it can come back in the same breast, in the opposite breast or in the lymph nodes around the original breast. If breast cancer has metastasized outside the breast, however, there are multiple sites that we look for. Breast cancer, as we mentioned, can spread to the bones, to other visceral organs including the liver, to the lungs and also to the central nervous system. It's important for us, as patients and physicians, to note how different these diseases actually are in terms of their pace, their biology and how they can be treated.

There are various modalities of treatments and multiple disciplines that we employ together. I am a medical oncologist who uses hormonal therapies, chemotherapies, medicines to treat breast cancer. But we work very, very closely with other physicians in other disciplines to help us as a team. So breast cancer patients will really have almost three doctors in terms of what is appropriate for them: a surgeon, who will work with us to see if any of the tumors can be excised or removed; and radiation to help with the chemotherapy or to try to palliate or relieve symptoms in very specific areas. We communicate with each other and try to integrate, as Dr. Rosenzweig is going to introduce to you, multiple modalities to try to support our patients.

There are multiple categories of hormonal therapy. I mentioned that if breast cancer is hormonally responsive, many of our treatments can forego chemotherapy right away, and we can try to see whether hormonal therapy will give us a good benefit. Another treatment modality that we need to employ, also for very specific treatment in areas of pain and areas that might have a risk for an event such as a fracture, for example, is

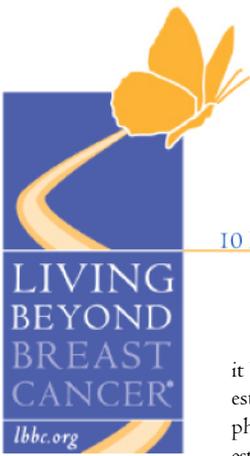
radiation. I'm going to briefly touch base with you, regarding bone disease, on the use of a nitrogen intravenous or oral type of compound called bisphosphonates. I'll get to a slide on this. These are very specific supportive treatments that can also help bone health in metastatic disease.

If the breast cancer has gone to other organs or if the breast cancer is not responsive to hormonal therapy, we would move to various types of chemotherapy. I'll go over just a few. There are multiple, multiple advances, and it is hard to fit all of the wonderful discoveries in the past few years into 20 minutes. I'll refer you to other websites, as well.

Now, chemotherapy – we could spend hours discussing the types, the side effects of chemotherapy. This may be non-specific, as we stand in the field now – non-specific, in terms of its effects on all of the body. We are trying to move toward targeted therapy. Breast cancers [are known to] overexpress different, very specific proteins that researchers and molecular biologists are now trying to target, either to add targeted therapy to chemotherapy or to use it on its own.

I'll try to focus on two specific receptors for which advances, with chemotherapy and without it, have been made: a HER2 receptor, which is overexpressed in breast cancer; and a vascular endothelial growth factor receptor, which helps tumors make new blood vessels. This is a very hot topic in breast cancer research.

We mentioned that if a breast cancer is hormonally responsive, we try to combat the tumors – whether they're in the bone, and usually if there is a low burden of breast cancer in the metastatic setting – with hormonal therapy. It's less toxic than moving to chemotherapy and still can give us a response in a reasonable amount of time. There are several different types, and I... want you to just focus in on this receptor right here – the estrogen receptor is what we are trying to modulate.



Tamoxifen has been around for decades, and it basically is a competitor of estrogen to the estrogen receptor. It's a lock-and-key type of phenomenon. When estrogen locks into its estrogen receptor, it sends a signal inside the cell, and the tumor grows. Researchers have tried to come up with compounds to fool the estrogen receptor, so the tamoxifen locks into the estrogen receptor and tells the receptor its place has been taken up, and the cell does not grow; that signal is not given inside the cell.

Similarly, aromatase inhibitors – there are several kinds; you may be familiar with names such as Arimidex, Femara or letrozole – actually prevent, in postmenopausal women, the conversion of estrogen pre-compounds from our adrenal glands, fat tissue and muscles. That prevents an enzyme from making more estrogen signals, and thus the tumor does not grow. Fulvestrant, a similar compound that is given as an injection, actually destroys the estrogen receptor in a competitive way.

All of those treatments together can be used in advanced breast cancer. We try to use them one at a time to see if we can get as much response as possible out of the aromatase inhibitors to lengthen the time of disease progression. We watch the bone health of our patients, too, because [the treatments] can pose a risk of osteoporosis. It's very important to watch for risk for osteoporosis.

I'm going to mention in this limited time many clinical trials, which are listed on the Living Beyond Breast Cancer website [<http://www.lbbc.org>]. It is an excellent resource that I would like to refer you to. It highlights many ongoing clinical trials and breast cancer news that are presented at national meetings. I have really appreciated how well it's put together.

One of the ongoing trials listed on the Living Beyond Breast Cancer website is a new theory of combining one of the aromatase inhibitors with this injectable fulvestrant. That's in clinical trials now. We haven't had a lot of data on putting two of them together; as I mentioned, they usually are used in sequence.

If the breast cancer has gone to the bones, this class of compounds called bisphosphonates – the clinical drug terms you might be familiar with, IV compounds, are Aredia or Zometa – usually are given once a month. This is a pretty complicated slide from the *New England Journal of Medicine*, but I just wanted to point your attention to two different types of cells in the bone: osteoclasts, which break down bone; and osteoblasts, which

build up bone. They both respond to local factors.

Tumor cells can stimulate osteoclasts to break down bone. That's what forms these spots in bone that can often lead to fractures, pain and need for radiation therapy. That's why we use these all together. As I mentioned, immune cells or even tumor cells can secrete a variety of hormones that will stimulate the osteoclasts, but the bisphosphonates inhibit that. They slow those types of destructive cells so the tumor cells and what the tumor secretes don't cause so much damage.

Again, whether a woman is getting chemotherapy at a different schedule or hormonal therapy, these bisphosphonates can be given on a once-a-month basis to try to prevent these skeletal-related events of metastatic breast cancer. That's another advance in the past few years in which these have been compared with each other. Many clinical trials have shown that some of the oral preparations, like clodronate or Boniva, might be used for osteoporosis, and they're in clinical trials to see whether they're as good as the IV preparations.

I mentioned that if a breast cancer is not hormonally responsive, or if there is a larger burden of tumor and the physician does not think the response from an aromatase inhibitor or other hormonal therapy would gain a good time of stability for the breast cancer, we will often move to chemotherapies. I listed six commonly used chemotherapies that are used in both early-stage breast cancer and advanced breast cancer. Many, many clinical trials are being done. It's a very exciting time to see what schedules are working better than the previous schedules and what some of the new ones are that are coming out.

I want to just point your attention – these are a lot of molecular vocabulary words, but the bottom line is that many of these named chemotherapy agents work in different ways to stop the cell from dividing. Some get into the DNA of the cell, whether they interrupt the way cells pull apart when they divide – that's what a microtubule helps to do; it's machinery that helps the cells pull apart when they divide – or they fool the cells in the backbones of DNA that it needs to replicate itself.

Chemotherapy is used either in combination, if the physician thinks a rapid response needs to be made and if a patient can handle the side effects of it, or one at a time. Many studies have been done and clinical trials have shown that the response rate can be just as good with one type

of chemotherapy at a time as with combinations. But, again, it's non-specific. All of the chemotherapies, despite how good they are, have a relatively non-specific way of affecting cells that are rapidly turning over. That's why there are a lot of different problems with side effects.

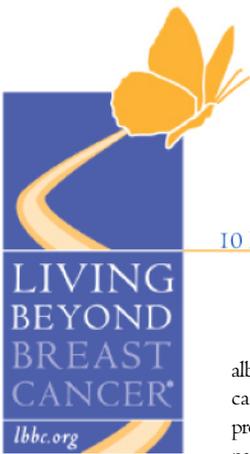
Some highlights on the Living Beyond Breast Cancer website, in terms of recent clinical trials: people are looking at different permutations of how the chemotherapy is given. Is it better to give it once a week, every three weeks, depending on the type of chemotherapy? Can we combine the chemotherapy with some of the targeted agents? That's what I was mentioning before that I'll show you as well.

These three that are highlighted on the website, what I'm just going to show you is that, for example, you'll hear a lot about taxanes: paclitaxel, which comes from the bark of a Pacific yew tree, believe it or not; and docetaxel or Taxotere, which has been widely used in breast cancers, both early stage and advanced stage.

... In the metastatic setting, it's been found that Taxol given at a lower dose but closer together – once a week [as opposed to every three weeks] – not only has a better side-effect profile but also yields a greater ability to keep breast cancer from coming back or from progressing such that chemotherapy needs to be changed. This was presented at a major meeting of the American Society of Clinical Oncology about two years ago. This is one we use in the clinical [trials] a lot – Taxol as a single agent once a week, for example.

Taxotere or docetaxel has been compared with Taxol by itself to see whether the time to progression is improved. These have similar side-effect profiles, which we will get to in terms of neuropathy and lowering of the blood counts. A specific study that was presented in the *Journal of Clinical Oncology* did show that the proportion of patients who had not progressed was higher on the Taxotere than on the Taxol. Those particular doses, though, were compared at the every-three-week regimens. That's another option that has emerged recently in clinical trials.

Taxol is known to have some side effects of causing allergic reactions. The tubing has to be very specific. We need to make sure patients get pretreatment with things like Benadryl, Tylenol or steroids to cut their risk of an allergic reaction. Recent research has sought to develop Taxol in a better-delivered system.



Taxol also comes in a preparation with an albumin coating. Albumin is a blood protein that carries all kinds of different hormones and proteins in our bloodstream anyway. That is called nanotechnology – a nanoparticle where Taxol is encapsulated in albumin. It causes better delivery to tissues with fewer side effects and less need for prophylaxis against allergic reactions.

[The albumin-coated Taxol] is called Abraxane commercially. It also has been compared with Taxol by itself, the every-three-week dose, and it has shown a better median time to progression. Abraxane can be given first; it also can be given after, if a breast cancer has become refractory to the taxanes. Several clinical trials have shown that Abraxane is also a very good option.

I'm going to have you keep this part in mind, because we need a lot of supportive therapy in terms of its side effects as well. Because more drugs in the nanoparticle can be delivered to the breast cancer, more side effects in terms of the neuropathy may occur. They may be a little bit more severe than the taxane alone but may last a shorter time.

I mentioned targeted therapy. Not only do we want to use chemotherapy to try to combat breast cancers, but we also want to become more specific in targeting emerging new knowledge about breast cancers. The HER2, or human epidermal receptor, family is a very important family of receptors that has been shown to be overexpressed on breast cancer. It's a family of four receptors. Basically, a sheet of fat lobules comprise the membrane of a cell, so it's the wall of a cell; it's the coating of a cell. They just fit together to keep things out of the cell.

HER2 is overexpressed in 25 percent to 30 percent of breast cancers. This little receptor sticks out from the surface of the membrane. It's sticking out, ready to capture growth signals and translate that through the core inside the cell to a whole mechanism and a whole cascade of factors that will tell the cell to grow. The HER2 being overexpressed often gives the cell multiple signals to keep growing. There is an antibody to HER2 called trastuzumab, or Herceptin, that you've heard a lot about in the news, I'm sure. When this antibody binds with that receptor on the cell membrane, it fools the receptor and the cell cannot translate those growth signals, so the growth will hopefully at least slow down, if not stop.

The advances that were made and published in the *New England Journal of Medicine* back in 2000, 2001, have shown that . . . progression-free survival is higher when trastuzumab is combined with Taxol, for example, in HER2-positive metastatic breast cancer. That is a standard of care. This is just to highlight that we're trying to incorporate more targeted therapies, either adding to the chemotherapy or using them alone.

An oral compound that is in clinical trials and hopefully will come out soon targets both the HER2 and the HER1. It's lapatinib, an important compound that also has prolonged time to progression, or TTP. Clinical trials have looked at it in combination with an oral chemotherapy called capecitabine. This is in HER2-positive breast cancer. Again, breast cancers all act differently, and in this particular situation of HER2-positive breast cancer, we can use that.

It's a very, very important compound, because it can cross the blood-brain barrier. I mentioned at the end of one of the first lists all of the different places breast cancer can go, and the central nervous system is a very difficult place to treat. We are making advances with that, however. Chemotherapy does not necessarily cross the blood-brain barrier; the brain is very, very protected. There are many challenges, but lapatinib has been shown also to help with brain metastases, and that is a very, very good and helpful advance.

A tumor cell can call in signals to make its own new blood vessels. This is an example of how tumor cells may secrete factors such that new blood vessels will grow around them. The mechanism they may use is called vascular endothelial growth factor. Tumors and even lack of oxygen can cause vascular endothelial growth factor to be released. That can act on blood vessel cells to make their own growth and to cause new blood vessel cells to grow around a tumor.

Significant advances have been made not only in breast cancer but also in colorectal cancer and lung cancer. When vascular endothelial growth factor is secreted by a tumor, endothelial cells can respond to that, grow and start to make new capillaries around the tumor, make new ways to make blood vessels. But an antibody has been developed to the vascular endothelial growth factor receptor: It's called Avastin, or bevacizumab. Avastin also has been combined with Taxol. This is in HER2-positive or HER2-negative breast cancers. This clinical trial particularly was done in HER2-negative breast cancers.

This illustrates our goal of not only utilizing the best chemotherapies but also trying to at least pair them with targeted therapy. Dr. Kathy Miller from Indiana and multiple late-breaking sessions at the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium have shown that when this antibody, given every two weeks, is paired with weekly Taxol, the amount of time we can keep a breast cancer from progressing in its growth has been lengthened by almost five months. This is very, very important. It has been looked at with other chemotherapy agents.

Also being developed – and used in kidney cancer – is a small oral molecule, called Sutent, that inhibits blood vessel growth factor. It also affects blood vessel growth. It affects other pathways. Even in patients who have had multiple rounds of different types of chemotherapies, a response rate was seen and gauged [by Dr. Miller in Indiana] after this oral compound was used even by itself. Clinical trials in progress combine this oral blood vessel growth factor inhibitor with taxanes, with Herceptin. Or, for a patient who has enjoyed a response and for whom things are stable, it's used as what we might call maintenance therapy to try to keep the cancer at bay for a while by concentrating on targeting the blood vessels.

Where the research is going to try to incorporate targeted therapies is very, very important. Targeted therapy is tolerated much better than chemotherapy. As you may know and might even have experienced, the side effects of chemotherapy are great. We weigh risks and benefits of the side effects of chemotherapy, which include hair loss, fatigue, nausea, vomiting and [gastrointestinal] side effects. These are all very general because, as I mentioned, the chemotherapy is not as specific as the targeted therapy.

There are many ways to combat this, but we need a lot better techniques in terms of supportive care to try to stave off these side effects. I also mentioned peripheral neuropathy. We've discussed it a lot at our institution, including how to combat neuropathy – numbness and tingling and pain – that can come with taxanes specifically. These are all areas of research where we need better medications and better ways of combating side effects . . . and helping our patients along.

That's all I have in this particular time frame, because I want to allow Dr. Rosenzweig to present to you [about] supportive treatment. We will be able to answer some of your questions afterward. Thank you.



MODERATOR:

Thank you, Dr. Morris. Our next speaker is Dr. Steven Rosenzweig. He is a clinical associate professor of emergency medicine at Jefferson Medical College. He graduated from the University of Pennsylvania School of Medicine and completed his training in emergency medicine at Thomas Jefferson University, joining the full-time Jefferson faculty in 1991. He served as founding medical director of the Jefferson Myrna Brind Center of Integrative Medicine from 1998 to 2005, and he continues as its academic director. Dr. Rosenzweig's clinical practice focuses on patients living with chronic illness and advanced medical conditions and treats cancer patients in all stages of treatments using integrative medicine to support, amplify and expand beyond the benefits of conventional treatment alone. Dr. Rosenzweig?

STEVEN ROSENZWEIG, MD:

My assignment is to talk about therapies that are added on to mainstream, conventional oncology approaches. I'll begin with a slide about Stephen Jay Gould, the famous Harvard biologist, who wrote this little essay. You can find it on the Internet if you just Google, "The Median Isn't the Message." He wrote this essay 20 years after he was given an eight-month prognosis from his cancer. Dr. Gould made the point about what the median is, and our statistics are given in medians.

Median is where most data points bunch up. . . . You can get a certain notion about things when you are focusing [where the data points bunch up] and ignoring the fact that there are all of these [other] data points out there as well. It's a very good essay to read, and I invite you to look at that. It is important to know, as we live with uncertainty, that . . . there are folks who have exceptional experiences and responses and continue to do very well despite advanced disease or with advanced disease.

Today I want to talk about integrative medicine and give you a sense of what it is. I'm going to give you three examples. These are kind of illustrative cases of using natural medicines to add in to optimal conventional medicine. I want to mention mind-body medicine and tell you what you need to know about it. Then I want to spend a few moments talking about strengthening your vitality, a sense of aliveness – what I call "strengthening the life force," a term that, although missing from conventional medicine, is quite fundamental to all other healing systems.

When we talk about integrative medicine, first of all, we're talking about incorporating all of these other approaches to healing that have historically been excluded from mainstream medicine: Chinese medicine, mind-body medicine, body-based techniques such as massage and chiropractic, energy therapies such as Reiki and electromagnetic therapies, and biological agents such as herbal medicines and shark cartilage, these other biological agents that are just not part of mainstream medicine. The first things we pull in from this arena are things that seem to make sense and that we feel can buttress conventional care.

Another way of looking at it is that not everything is black and white. When we look at clinical studies published in the *New England Journal of Medicine*, we begin to have sort of absolute clarity. But another thing we do in integrative medicine is, we look at areas where there is a lot of evidence that can be sorted through and where we feel it is useful to pull approaches from – even though the final tests and the final research have not yet been done – because they're nontoxic approaches and they make sense to incorporate. And definitive trials will never be done, because it's not a funded area of research. I'm going to give you a few examples.

Integrative medicine has expanded to actually form a feel of integrative oncology or integrative cancer therapies. There are two journals out, which are . . . interesting to look at as a patient, particularly Keith Block's journal, *Integrative Cancer Therapies*. There is a Society for Integrative Oncology for healthcare professionals. The scene is kind of changing, and this arena is just beginning to emerge.

Natural medicines – what do we mean by "natural medicines"? It's a little bit of a hodgepodge term that I want to decode. . . . The [Food and Drug Administration] chooses to label some things as drugs and some things not as drugs. Homeopathic medicines that might contain nothing but sugar water are labeled as drugs by the FDA, but most herbal medicines and vitamins and nutrients are labeled as food supplements.

In integrative medicine, we're looking at herbal medicines, vitamins and nutrients and other stuff that, although the FDA allows it to be sold in health food stores, doesn't really look like a vitamin or an herb. One example of that is the hormone melatonin. You can go into any vitamin store and buy melatonin in a bottle. It's a hormone made by the pineal gland in the middle of our brains. It's made at night. It makes us groggy and sleepy. If

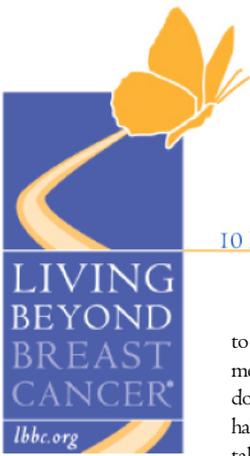
you are exposed to a lot of bright light in the evening, you won't make so much of it and you won't get drowsy. It has a lot of interesting history and use in cancer.

People use low-dose melatonin as a sleep aide or to help with things like jet lag or shift work, but I'm talking now about the use of melatonin historically in cancer. Dr. Lissoni – I'll be showing you his work in a few minutes – has researched this quite a bit. Now, I knew Gloria was going to show you complicated slides, so I had to show you one complicated slide. Here is the pineal gland in the brain. It likes to make melatonin. Sunlight inhibits that, so we don't make it during the day. Happiness promotes it, so nice mood increases your production of melatonin. Sunlight diminishes it; so you want to have your room nice and dark and use candlelight in the evening to help yourself along.

There are two things you need to know about the effects of melatonin for the purpose of my discussion. One is that it stimulates the immune system through various mechanisms. The other is that it stimulates the bone marrow through various mechanisms. It has immune system-enhancing effects and bone-marrow and blood-cell production effects.

Now, trying to pull together the experience of Paolo Lissoni, Dr. Lissoni in Italy . . . [this slide] is a distillation of the many studies he's published. He's studied thousands of patients in controlled, clinical studies. Based on his clinical trial work, it looks like taking high-dose melatonin with conventional chemotherapy or melatonin with immunotherapy – interleukin-2 is the example that was studied – might improve tumor regression rate in patients with breast cancer and other solid tumors. Also, combining melatonin with chemotherapy in patients with metastatic solid tumors seems to increase regression rate and one-year survival rate by approximately 50 percent when compared with chemotherapy alone in those particular studies. We're not talking about the chemotherapy-plus-Avastin trials. We're talking about, within these settings, showing an added, independent effect of melatonin.

The addition of melatonin may reduce chemotherapy toxicities, including low blood counts, weight loss, fatigue and neuropathy. People tend to feel less anxious when they take the melatonin. There's preliminary evidence that melatonin might improve stabilization rate and possibly survival in patients with resistant or untreatable tumors that are no longer responding



to therapy. It may be worthwhile simply to add melatonin at that point. We're talking about high doses. If you want to go to sleep, you might take half of a milligram, maybe three milligrams. We're talking here about 20 milligrams taken only at bedtime, or you'll mess up your sleep-wake cycles.

For example, a paper published in the *British Journal of Cancer* ten or 11 years ago looked at adding melatonin for breast cancer patients who were on tamoxifen but were progressing. In this very small study of 14 women, when you added melatonin, you got a partial response in 28 percent of the women. In 60 percent of the women, you saw a stabilization of disease. It didn't matter whether you were estrogen-receptor positive or negative. In patients progressing on tamoxifen, when you added melatonin in this very small cohort of patients, there seemed to be some activity by the melatonin.

Another example is patients with low platelet counts. We need platelets for blood clotting. If your platelets are low, it's a problem because you have a bleeding tendency. What they did here was take another small cohort of patients – 14 patients with metastatic breast cancer and persistent low platelet counts – and they were able to complete another four cycles of their various chemotherapy regimens with the addition of the melatonin. At two days, the average platelet counts were already up. At seven days, with the addition of melatonin, it was already up to the normal range. It was a very fast effect – perhaps some added effect in terms of hormone therapy; perhaps some bone marrow protective effect with the addition of melatonin.

A study of toxicity and efficacy during cancer chemotherapy involved patients with various solid tumors who had advanced symptoms and were really fatigued and not able to do very much. This was 250 patients, and 77 of them had breast cancer on various chemotherapy regimens. They were given the best regimen for them. They were randomized to get either chemotherapy alone or chemotherapy plus melatonin. When you added melatonin in this study, you saw a statistically significant increase in regression rates, in time to progression and one-year survival and diminished treatment toxicity.

Does this prove that melatonin is an effective cancer treatment? It doesn't prove it the way we think about proving chemotherapy or proving oncologic treatments in the United States in terms of FDA approval. Does it suggest that melatonin might have significant activity and benefit in

addition to optimal conventional care? I think it does suggest that melatonin may really have a role. It appears to be nontoxic. It appears to reduce symptoms and side effects. I'm trying to give you an example of something that appears to be useful. It should be prescribed and taken under physician supervision and in coordination with the treating oncologist who's captain of the ship. It may have an important role.

Avemar – who in this room has heard of Avemar? Oh, good. Avemar is manufactured in Hungary. It is a fermented wheat germ extract. It's widely available in the United States under the label Ave. They have a nice website. Google the word "Avemar," and you'll get to the website [<http://www.avemar.com>]. What do we know? We know that in cell culture, it will increase breast tumor death in cells exposed to tamoxifen. In animal models, you see increased killing when in combination with vitamin C; you see increased tumor killing when combined with chemotherapy agents; and you see improved immune function.

In clinical models, no breast cancer study has been published, but studies were published in oral cancer and in colon cancer. Stay with me as I make this link. We have a food product that's fermented wheat germ extract, seems to have interesting activity in animal models, appears to be nontoxic – and I'll share some of those data with you also – and has not been studied in breast [tumors] but has been studied in other solid tumors. I'm going to give you an example of that right now: colon cancer.

I know this is a breast cancer conference, but there's the data. Gloria will tell you that these chemotherapy agents that she's discussed are also used in other tumor types. In the *British Journal of Cancer* in 2003, this paper was published [that was] very interesting. It involved 170 patients. Patients either got standard treatment for their colon cancer, or they got standard treatment for their colon cancer plus wheat germ extract, Avemar. [The trial] was non-randomized. I'm going to tell you about that in a minute.

The data [showed that] there was a new recurrence of tumor in 3 percent of the Avemar group versus 17 percent of the control group. There were new metastases in 8 percent of the Avemar group versus 23 percent of the control group, [which had] no wheat germ. There was significant improvement in survival curves and disease-free survival curves.

[A trial being] non-randomized is a problem because it means the two groups may not be the

same, and, indeed, they were not the same. The folks who wanted to take wheat germ extract had more advanced disease to begin with. They had had colon cancer for a longer period of time. They were at a worse starting point, and they had a much better outcome when wheat germ was added. I wondered ... [whether] you might see a larger treatment effect if this was a randomized trial, but we don't know because we don't have those data.

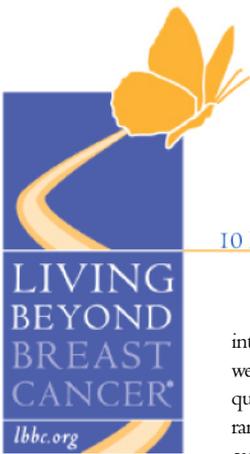
[That's] another example of a health-foods store item that looks like it can be added to standard treatment and perhaps improve outcomes in a significant way. It's a yellow powder. It's not delicious. You mix it with water. It's taken every day. In breast cancer patients, [no data are] published in a peer-reviewed journal; this one guy reported his experience of 55 patients, and he says they felt better on it and had fewer side effects.

I can tell you my patients who take this, except for complaints about what it tastes like, do very well on it. It's just like patients who take melatonin. Some feel too groggy and knocked out on the melatonin, so they don't take it. Here, some people don't like the taste, so they stop it. Generally, it's well-tolerated.

An herbal medicine that I have a lot of experience with is European mistletoe. It's the white-berried mistletoe, not the red stuff that we kiss under in the United States. It's the most commonly used herbal medicine in cancer in Europe. It's been used since the 1920s and is used in Germany alone by about 400,000 people today. Many mistletoe products are on the market. Iscador, one of the brands, is an injectable medicine made from the whole plant.

It's a subcutaneous injection. The patient usually gives it to herself, although a family member can do it. It can be given anywhere a subcutaneous injection is given. Sometimes you get a little red spot at the area. We use this often; we think about this in combination with chemotherapy or standard treatment and radiation therapy. There are models that show enhancement of immune function when this is given, but the effects may not be limited to its immune effects.

In 2003, I was a member of a group that published this review in the *European Journal of Medical Research*, and we looked at all controlled trials in mistletoe that had been published up to that point. It's basically the same today; really, nothing has been added. We found 16 randomized clinical trials and two quasi-randomized [trials]. That means that on Mondays people were entered



into the mistletoe arm, and on Tuesdays people were entered into the non-mistletoe arm, so it was quasi-randomized. Then there were five non-randomized studies. Four of these included breast cancer patients.

These were broad studies of multiple tumor types. What we found was that 12 of these 16 studies showed statistically significant, positive results in these areas: survival, remission, quality of life and treatment-related quality of life. In 12 studies, each one had one or more of these parameters showing statistically significant results. Seven studies showed positive trends, but they were not statistically significant. One study showed a negative trend – again, not statistically significant. I need to emphasize that there were methodological problems with all of these studies; these were not terrific studies.

[Dr. Patrick] Mansky is beginning to study this at the [National Institutes of Health], using mistletoe beginning with phase I. We are waiting for additional information. In the meantime, this is a medication that appears very well-tolerated. The National Cancer Institute has reviewed mistletoe on its website [<http://www.cancer.gov>]. You can look at its safety discussion. It is not touted as an effective cancer treatment, but you can see that it's a nontoxic treatment.

We're not going to talk about supplements because I don't have time, but I recommend that you check your vitamin D level if it hasn't been checked, because vitamin D has particular anticancer effects. Many of my patients have vitamin D deficiencies. I recommend high-normal levels of vitamin D. Some of my patients are vitamin A deficient, and you might want to check that; have your doctor order that.

If you're taking a statin drug, check your CoQ10 level or take CoQ10, because statins reduce the body's ability to produce CoQ10, which may be an important nutrient in [fighting] breast cancer specifically. Some preliminary data show that CoQ10 may play an important role. Statins will reduce tissue levels of coenzyme Q10.

Mind-body – what you need to know is that it appears that the mind is related to the body; it's not separate, and it has real effects when we use mind-body practices. A book written by Jon Kabat-Zinn called *Full Catastrophe Living* defines mindfulness-based stress reduction, mindfulness meditation and the program that we offer at Jefferson.

We find that, for women and other folks with cancer who learn this meditation practice, it's useful in all stages of treatment. It reduces anxiety, increases mood, increases energy, has interesting immunological effects and certainly improves the sense of control over one's life and moment-to-moment experience. Whereas reality is what reality is, it helps settle and drop down into a space of greater stability and calm. These practices are very learnable, very worthwhile and have palpable effects. That's our program. [You can] call 1-800-JEFF-NOW for our mindfulness program. We also have support groups.

... Finally, the last few words: When I say "life force," do you know what I mean? Do you have a sense of what I mean? We're alive. We're filled with an energy of experience. There are days when you feel you don't have much of it, and there are days when you feel you're brimming. This is what I mean by strengthening our life force. Other healing systems called this qi or prana. You can call it vitality. Yes, we're dealing with symptoms. Yes, we're dealing with treating. How do we support ourselves in our energy level?

We're talking about attention to food that is filled with life force and key nutrients, and [attention] to certain therapies that are intended to balance, harmonize, support resilience, whether it's massage or acupuncture or these adaptogen herbs – this is eleutherococcus, or Siberian ginseng. Certain herbs themselves can be combined safely with cancer treatment and support one's sense of energy and well-being. These approaches can also be used for symptom management. Perhaps during the question-and-answer section, if we're talking about symptoms, I can talk a little bit more about that.

What I set out to do was tell you that there is this field called integrative medicine. The idea is to bolster and expand optimal, conventional care with additional approaches and use things that we know are safe, [for which] we feel there's a body of evidence so one can build a case for using them in a rational way, and that appear to really be of benefit. They're a benefit perhaps not only in treating the tumor but also in overall well-being and certainly in experiencing a greater sense of stability, calm and energy and in supporting life from day to day, week to week, month to month and year to year. I thank you for your attention, and both Gloria and I are here now to answer some questions. (Applause)

WOMAN:

Dr. Rosenzweig, you had mentioned Avemar and Iscador used in conjunction with your regular remedies for cancer. What if you're in remission? Can those two substances be helpful?

STEVEN ROSENZWEIG, MD:

The question is whether things like Avemar, the wheat germ extract, [and] Iscador, which is a European mistletoe product, can be useful in maintenance treatment for persons in remission. I often think they are useful. We have limited data on this, but it appears in some folks to be of benefit. There are lingering effects from these treatments – chemotherapy and radiation therapy. After treatment is a time for recuperation, convalescence, recovery, rejuvenation and repletion, and it's a good time for taking things that support immune system, [that support] antioxidant repletion. If these things are helpful in supporting immune function, it probably is worthwhile even from that perspective.

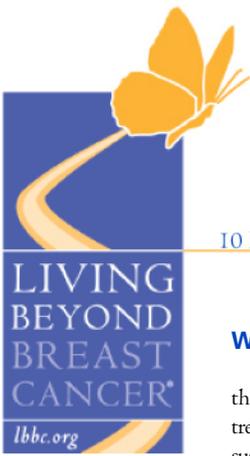
WOMAN:

Dr. Morris, a comment. I understand that at Duke University, they're undergoing work to create a test of taking a person's tumor ... to decide which chemotherapy agent would best treat the tumor. Does this work only on tumors, say, in an organ such as the liver or the lung? Or could this work on a person whose tumors have advanced in their bone?

GLORIA J. MORRIS, MD, PhD:

It's an excellent question. We're wondering in further research whether a tumor – whether it's a primary tumor or one that has metastasized – can be tested for chemo sensitivity. It's an excellent research question. I'm not aware of the study at Duke. Various clinical trials are being done in other organ systems, however. Whether this can be done on tumor cells that can be isolated from the peripheral blood would also be a very good research question.

In early breast cancer, sensitivity and even the risk of recurrence can be tested from the original specimen that was removed from a breast, for example, to see whether a woman might need chemotherapy at all or whether the breast cancer is hormonally responsive enough, if that's going to be the primary armamentarium we can use. Those types of tests are available. I'm not familiar with the chemosensitivity, but that's something we should look out for in clinical trials.



WOMAN:

I've read a lot of information about diet and the role diet plays in cancer prevention and treatment. I've seen a lot of information about sugar and how that encourages cancer growth. I've seen a lot on organic produce and pesticides in our food system. I've seen a lot on vegan diets. If you'd like to respond to any of those things, I'd be interested to hear your opinion.

STEVEN ROSENZWEIG, MD:

In answering your question about diet, it's a huge area that I can't do that much justice to in too short of a time. I can say . . . that I begin with a diet that is healthful and could be helpful for anybody because it is rich in antioxidants, is anti-inflammatory, promotes good immune molecules and doesn't promote the bad immune molecules in the body. This is [primarily] a plant-based diet that uses whole foods and is clean. You can detect pesticides in the urine when you eat a normal diet, and you can see those pesticides go away when you switch to organics.

The blood sugar is pretty constant in the body, but when you eat a lot of concentrated sugars – we tell our patients all of the time, every patient – you get a lot of insulin production. That predisposes you to metabolic syndrome and diabetes. The overproduction of insulin and insulin growth factors might play a role in the tumor environment.

The idea of the diet is to support health and also create a milieu, an internal milieu that is unfavorable to the tumor and favorable to the immune system. An anti-inflammatory milieu, a milieu that's rich in antioxidants, and perhaps a milieu in which there is modest and not excessive insulin production might be useful. That's a diet I put my heart patients on, I put my diabetic patients on, I put everybody on. There appear to be some protective effects.

That fundamentally healthful diet can be narrowed and amplified in a couple of different directions: raw foods and macrobiotics. It makes sense at certain times and for certain people to move in that direction; there certainly are times and people in which it makes no sense to move in that direction. The decisions must be highly individualized. If you want to learn about macrobiotics, the Kushi Institute [<http://www.kushiinstitute.org>] in Massachusetts [is a good resource]. If you want to learn about the vegan or the Gerson diet or

the raw foods diet, Hippocrates Institute [<http://www.hippocratesinst.org>] in Florida is another good resource. Thanks for that question.

GLORIA J. MORRIS, MD, PhD:

. . . We're not sure of the effect of antioxidants. We don't know the effect of antioxidants on the infusion of that chemotherapeutic agent that day, but to support our patients when they're recovering from chemotherapy or their blood counts are coming back up, that's the time when we would look for supplementation in terms of vitamins, iron supplements, things like that. I certainly do rely on our colleagues. If there is an integrative medicine department in your area or at your university that could be worked with, that would be very, very helpful.

WOMAN:

Do you have any other comments on ...?

GLORIA J. MORRIS, MD, PhD:

Supplements – it's a very large topic, and we could spend some time on very specific supplements to add. We also need consultation in terms of helping with neuropathy, and that's a whole other topic that we could get into. Other supplements that we've tried in anecdotal regimens that we can try as infusions with chemotherapy – those are things we've also been trying to think about.

WOMAN:

Do you have any comments on integrating supplements?

STEVEN ROSENZWEIG, MD:

Were you also talking about discernment among the conventional trials? Or was it both? . . . This is tough. Patients often find themselves in a squeeze here. My own observation is that there are many fine cancer centers, but there's wide variation in the openness and interest in embracing the integrative approach. I've had patients work with cancer specialists who are very reactive and hostile toward the idea. I've had the same kinds of patients, same situations, same treatments, who are working with oncologists who were quite open and flexible around this approach. It's more of a sociological variation, I think, than a scientific variation. It's just really common on the medical team, and finding a team that can work with you and respond to what you're looking for – I think that's quite possible.

GLORIA J. MORRIS, MD, PhD:

. . . That response that I gave is basically what I've learned in training, and we don't have a lot of data on that. We're also, as physicians, wanting to do the safest thing possible, wanting to give pure treatment without anything else interfering with what we know is being infused that day. That is, without a lot of data to back that up, what I have been taught and what I'm telling my patients at this time, just because we don't know the effects of the infusion on that day.

GLORIA J. MORRIS, MD, PhD:

. . . Yes, because the likelihood of the metabolism and the half-life of the drug has often been eliminated at that point. The anticancer effects certainly will persist, as we've mentioned earlier, but to try to provide those types of nutrients and build back up the bone marrow, things like that, I'm very comfortable with. You see that physician and patient, we both have different levels of comfort that we work together on as a team – comfortable with the data we know and comfortable with the unknowns as well – so we often arrive at the conclusions at a rate together.

STEVEN ROSENZWEIG, MD:

Can I add to that? First of all, just to emphasize again that there's more to supplements than antioxidants. Number two, antioxidants in food are ten times more bioavailable to the body than antioxidants taken by mouth, [such as] capsules. Number three, it seems to me that certain agents work in a way that maybe could interfere with antioxidants, but other agents, like the taxanes, have a mechanism of action that has no relationship to antioxidants. I feel like, in that area, it's not even relevant.

Number four, there have been interesting review articles on this topic that I often tell my patients to read. A book written by Ralph Moss is pretty up-to-date on antioxidants and chemotherapy. There was a review article, which is available through Medline [<http://medlineplus.gov>], published in *Integrative Cancer Therapies*. I showed you Keith Block's journal. It's useful to read what has been looked at and the information that's around.