

**CANCER
SURVIVORS**
SYMPOSIA SERIES
Issues & Solutions for Life After Cancer

**Living With "Survival:"
Long-Term Effects of Cancer and Its Treatment**

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**Long-term Considerations After Chemotherapy & Stem Cell
Transplantation**

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It's great to see so many familiar faces, some old friends, and new ones. Thank you for coming tonight. This is a very important thing. Long-term followup and long-term complications after chemotherapy and transplant actually are very near and dear to my heart. Despite all the time I spend doing much of the acute care, my own parents are 30-year survivors of Hodgkin's disease and endometrial cancer. That truly shaped and informed many of my decisions in terms of how I practice medicine, what kind of medicine I cared to practice, and how I sought to carry that out. I think that we've seen with them many of the things that we need to consider, struggle with and be concerned about, with problems with function, neuropathy, Parkinson's, secondary cancers, memory and many of the social issues that do occur after we've survived cancer. I'd like to address some of those today using both stem cell transplantation or high-dose chemotherapy, as well as standard-dose therapy, as an illustration of the different issues we need to watch.

It's been phenomenal watching the development of stem cell transplantation. I've been involved with this since 1986 as an intern. I took care of the first stem cell transplant patient at New England Medical Center and, at that time, that was a scary thing. At that time it was the last thing. It was the Hail Mary pass of medicine. Now this is something that we can now do as part of our initial planning of therapy for people with multiple myeloma, for children with different kinds of cancer, and to see it grow and develop in such a way from being one-size-fits-all to tailored therapy has been exciting. This is a treatment that started with the nuclear age. We saw that with radiation, atomic bomb victims, the

marrow was the most likely thing affected, and some government researchers found that if we took mice that were compatible and rescued them with bone marrow they survived. So we started using it in people. It wasn't until 1958 that E. Donnall Thomas, who won the Nobel Prize for stem cell transplantation medicine, did the first successful transplant for identical twins. This was a young girl, 4-years-old, with acute lymphoblastic leukemia. At that point, there were no treatments in 1958. The survival was measured in weeks. This girl received radiation, total body radiation, more of which you will hear from Dr. Anscher, and she then received bone marrow from her identical twin sister. This girl lived for three months. That was a lifetime at that time. She died of a relapse, because we know that radiation alone is not enough to cure acute lymphoblastic leukemia, and it wasn't until we started adding chemotherapy to the radiation that stem cell transplantation started to take off as a true promising treatment. We're starting to see things starting to pick up now, using bone marrow harvesting, and standardizing how we do this – in 1989 using peripheral blood stem cells; using cord blood transplant; and then starting to actually tailor the treatment specifically to the patient and their disease. These were all things that were true developments that allowed us to be more successful and bring this life-sustaining and lifesaving treatment to more people.

There really are two kinds of transplants, based on the source of the stem cells. Autologous, where the patient serves as their own donor, allows us to give patients a higher dose of chemotherapy than they would normally be able to withstand because their bone marrow would not tolerate it. So, by taking some of the stem cells, putting them in a safe place, giving them a large dose of chemotherapy, we're able to be more effective against the cancer we're trying to treat, but rescue the bone marrow from this lethal dose of chemotherapy.

Allogeneic stem cell transplant is where we identify a donor that matches, either within the family or perhaps from the volunteer donor pool, or perhaps from an umbilical cord blood source, again, either from a family member or from the volunteer donor pool. This is high-dose chemotherapy, but it brings with it the most powerful form of immune therapy that we have in cancer. We talk about it as perhaps the donor going in and doing renovations, renovating away the leukemia, renovating away the lymphoma, being more specific to be more effective against the lymphoma or other cancer we're trying to treat.

The indications for stem cell transplantation has been increasing over the years. You can see many of the cancers we've been treating and, in fact, we've gotten better at it to the point that we're now trying to treat conditions that are not malignant. Perhaps conditions like sickle cell anemia where we know that high-risk patients are going to have a significant impact on their life. But by intervening and trying to fix the problem before it starts, without causing more problems, we think that we can make a better impact on the overall long-term, not only in survival but quality of their life as well.

The annual number of blood and marrow transplants. This actually only goes to 2002, but it actually has started to rise again. This dip was when we realized that perhaps we were not doing women with breast cancer as much of a favor by giving them an autologous stem cell transplant. But since then, other indications such as multiple myeloma and some of the pediatric cancers have brought it up to the point of almost in excess of the 40,000 per year that we've seen. Allogeneic stem cell transplants have also increased because we're now looking at a more tailored way of treating stem cell transplant patients. Having more access to more donors, using umbilical cord blood transplants and, again, offering this lifesaving treatment to more people.

As you see, the sources are increasing. We're seeing more cord blood transplants for younger people. Actually, it's even happening in older patients as well. And more use of peripheral blood stem cells, which is more of a reason that access is happening to patients over age 20 and, actually, even up to age 70. I have a new definition of young, and as I get older, it gets older too.

We are going to talk about the long-term complications of chemotherapy and transplant. You may be saying, Dr. McCarty, I just went on that ride, I don't want to go on that one again. The point is that we're not here to tell you about how, after having done so well, that things are going to fall apart. The idea is to really take charge and control, to recognize, because knowledge is power. I'm going to be talking about some things where we need to be concerned. Just as you need to take an active role in your therapy as you've done already, that's what this time forward, as Dr. Dunn has talked about, that we're going to be talking about as well. So we're going to talk about the complications that occur because of the specific kind of chemotherapy or radiation, or that may happen from a complication of transplant called Chronic Graft-versus-Host Disease, or from immune suppression or the immune system not being quite where it was to start with. Fertility. Some of the things that Dr. Dunn touched on with pulmonary and cardiac problems and secondary cancers. But we're also going to talk about the social and psychological impact of having gone through this treatment and working it through now.

Bone Loss. Avascular necrosis is essentially an injury that happens to certain bones because the blood supply is compromised in that area. Usually it happens in the hips. It is associated with use of steroids, either a low dose for a very long time, or the use of very high doses for the treatment of different sorts of disorders such as multiple myeloma and lymphoma. Again, it happens mostly in the hips, partly because of the anatomy of the blood supply in the hips, but it's more than that. You can get bone thinning in 50 to 60% of patients, and it may actually lead to the diagnosis of osteoporosis in 20%. 1-5% may actually end up with fractures. It's not just with steroids, but some of the newer agents such as the aromatase inhibitors for breast cancer may also be associated with osteoporosis. Additional risk factors that may pile on this as well are: a family history, many of us have parents that have had osteoporosis; low testicular/ovarian function because the results of chemotherapy or surgery may also further make this more

prevalent or worse; use of the growth factor G-CSF, or Neupogen, over long periods of time, because chronically low counts may also contribute to bone thinning; and, then, kidney dysfunction because of regulation and the way the body handles calcium and handles Vitamin D.

What can we do about it? One thing is exercise. If I have been involved in your care, you know that one of the things that I do is that I walk into your bedroom, turn on the lights, and threaten you with Nurse Ratchet to unmake your bed and make you walk the halls. There's a reason for that. One of the most important things that you can do is exercise. There's a study that showed that especially if you're on steroids and you're sedentary you could lose not just bone mass, you could lose up to 3% of your muscle mass every day. You can imagine how long it takes to come back. Yes, we can use bisphosphonates, many of the agents that some people probably in this room are on either for the treatment of multiple myeloma or for osteoporosis, and taking Calcium and Vitamin D. But exercise is probably the most important thing, not just during and after stem cell transplant, but during and after your chemotherapy. It's a prime example of "if you don't use it, you will lose it."

Hormone replacement therapy. Certainly hormones do have – the estrogen and so on – a direct relation to bone health. I'm not advocating that every patient should go on hormone replacement therapy because that risk/benefit must be individualized to why you need it and what you may have reached this low hormone state to begin with. The role of androgens, or male hormones, in this process or whether replacing them is effective is not yet a known, but that's going to be probably the source of future studies.

Gonadal Dysfunction. Therapy-related menopause is very frequent. It can happen because of doing it on purpose as part of the treatment for a cancer, but it also can occur from certain high-dose chemotherapies – Cytoxan alone, and this is actually commonly used with radiation, and the combination may actually induce poor ovarian and testicular function. So patients may notice absent menses, insufficient sperm production, and it is certainly more often after radiation. But it isn't just whether or not you're having menses or whether or not you're making sperm, sexual dysfunction is more related to Graft-versus-Host Disease. Many people may find that it is uncomfortable because of changes that can occur after the immune response. People with testicular cancers, in looking at long-term effects, actually fewer people with testicular cancer perceived having sexual problems than people with normal controls. So it's not a given. It's not a certainty. However, hormonal changes still can be an issue in that there can be loss of lubrication, there can be thinning of the mucosa, and low testosterone levels both in men and women can be associated with lower libido. It's certainly something that can be embarrassing sometimes to talk about, but it is something where there are interventions, in talking to your physician or talking to your gynecologist, that can be reversed so that we can enjoy the entire realm and the entire range of human experience.

What about fertility? Infertility doesn't always happen and recovery can sometimes occur. You can't assume that you're infertile. You can't assume that you can't have children. There is no evidence that pregnancy, for example, after early breast cancer, can compromise survival. But the decision to have children may be more related not on whether or not you can or can't, but more related about questions of being a parent and what your risk of recurrence may be. There is no evidence that your offspring, for women who have had breast cancers, have any deleterious effect of having their mother having gone through chemotherapy. These are things that need exploration, but certainly they are things that are very often hard to talk about or perhaps just very scary to talk about but, again, knowledge is power. Not always a contraindication.

Graft-versus-Host Disease is unique to stem cell transplantation. Specifically allogeneic, where you're using stem cells from another donor. This is when that immune therapy response is too much of a good thing and the immune response is now starting to attack part of not just the malignancy but part of the normal organ functions that we certainly want to keep. And it has a big impact on the quality of life after stem cell transplantation. It happens about 30% of the time in some large or small amount from a family member transplant, and in as much as 60-70% when an unrelated donor is used as the source of the stem cells. It can present in many different ways. In the skin, hair loss, nail changes, and thinning hair. Skin changes that look different, perhaps either thicker or color changes. In the mucous membranes with dry eyes, dry mouth, less saliva so there is an increased risk of dental caries. Vaginal dryness, in the GI, dry swallowing, perhaps liver problems where your bilirubin may be abnormal or perhaps you're not absorbing food and nutrients quite to the same degree. With the lung, something called bronchiolitis obliterans, which is essentially a form of more accelerated emphysema that can occur, and other things called polyserositis. Sometimes where the quality of life impact is not just the way this makes patients feel, but also the fact that we need to continue on the immune suppression and need to continue to be under active therapy can sometimes certainly impact the quality of patients' lives. This clearly is not a black and white thing. There are degrees of this involvement. A little bit is a good thing. Too much, however, is not. Fortunately we have many more tools in our armamentarium to try to bring this under better control and to make this complication come to an end.

Pulmonary risks. Certainly, again, in transplants where we use a brother or sister, or a volunteer donor, Graft-versus-Host Disease can affect the lung. It's an immune-mediated reduction in lung function, very similar to emphysema or chronic obstructive pulmonary disease. Chemotherapy, as Dr. Dunn has talked about, can lead to pulmonary fibrosis associated with bleomycin – it's 5-10% in people with testicular cancer where bleomycin has been used. It can occur years after prolonged use of carmustine for some of the central nervous system tumors. Busulfan is usually used in stem cell transplantation and can certainly be a concern, but now that we have a better way of individualizing the dose to individual patients we've actually seen a drastic reduction in this agent causing pulmonary toxicity. After surgery, patients may need to have a lobectomy, or a

portion of the lung removed. In this situation you may actually lose some lung function. It may be that you develop a fungal infection and that section of lung needs to be removed, or possibly the pleura, the lining around the lung, may either be tethered or may become thickened. This may interfere with the ability to exercise and exercise tolerance. These are all things, though, that can sometimes have a reversible component to it and warrant follow-up if these are symptoms that people are having.

Cardiac risks. Radiation to the chest is a concern but it also depends, and Dr. Anscher will talk perhaps more about this, it's not just the location but perhaps how the dose was delivered and in what areas. There often can be a sparing. But it's not breast only radiation, but certainly thoracic chest radiation. In testicular cancer there may be a couple of different reasons that someone may have an increased risk of a heart attack. Cisplatin, the heavy metals that Dr. Dunn talked about, can actually affect the vessel walls in the coronary arteries, increasing the chances that there may be clot or plaque formation and the formation of a thrombus. The hormonal changes after orchiectomy can actually increase the risk of clot and of abnormal lipids. This is best illustrated by something called Metabolic Syndrome, something that one of our own endocrinologists here has described very well. Metabolic Syndrome is insulin resistance, so higher blood sugars, or what we call adult onset diabetes, hypertension, high blood pressure, high lipids, and "this" (abdominal obesity). Basically, it leads to a 2.8-fold risk for an MI after chemotherapy versus someone who just had surgery. So this is something that warrants therapy. It isn't just, "Oh, well, I'm not getting around as much and these are just changes associated with old age". These are all things that, put together, actually represent a coordinated syndrome that does warrant intervention for each of those things. Control of the high triglycerides and the high lipids; control by exercise; control of the high blood pressure; and control of the diabetes may further reduce the risk of myocardial infarction. This is reversible. Congestive heart failure can be seen with some of the chemotherapies with anthracycline doses, and in the doses that I use in stem cell transplantation, chemotherapeutics that don't usually cause cardiac toxicity may in less than 5%.

Infection Risks. This actually can occur while you're going through chemotherapy, but after transplant sometimes it takes a while for immunity to come back to normal. It can also be seen now with newer agents that we're using for the treatment of CLL, in some of the lymphomas that affect the T cell or a B cell lymphocyte function. Fludarabine, cladribine, clofarabine, 2-CDA. I don't have any epipodophyllotoxins that Dr. Dunn has, but many of these agents do. There are many antibodies that actually affect T cell function that may reduce the immunoglobulin levels. For T cell lymphomas there are agents that actually go after the T cells, and this may lead to a long-term reduction in the normal agents of the immune system, as well as the cancers. Early, the problem is more related to mucositis and to bacterial infections from neutropenia. Late it may be more fungal, viral and encapsulated bacteria. For stem cell transplantation, not an autologous transplant, but for an allogeneic transplant, it may take up to two

years for the immune system to fully reconstitute. If you have Graft-versus-Host Disease, this may be longer.

It is very common for patients to have low immunoglobulins. The splenic function may not be normal. That's a very important organ in the immune system. Some people need to go on prevention for a variety of different organisms for quite some time. 20-50% might have shingles or herpes simplex reactivation. And PCP, something we usually associate with HIV, can even occur up to one year after transplant. It can also occur after the use of some of these other agents – fludarabine, 2-CDA, and clofarabine, that we've discussed that are used in standard chemotherapy as well.

What about secondary cancers. As Dr. Dunn very well illustrated, not just in children but in adults there can be as much as a 4 to 11-fold increase in the general population, and the cumulative incidence is 10-12% at 15 years. It's not all the same thing, as you may see here. First we worry about lymphomas within the first year, leukemias may be the next or myelodysplasia which is an injury to the bone marrow which could lead to either bone marrow failure or to leukemia, and solid tumors really are long latent with their most significant occurrence after 10 years but may occur out to 20 years. What is a solid tumor? In my patients I think about skin cancers. I think about abnormal pap smears leading to cervical cancer. I think about colon cancer. I think lung cancer. Things that could be related to the intensive chemotherapy or the use of radiation therapy. But it also can be due to the immune suppression. For example, the Epstein Barr virus may reactivate and, if it persists at a low-level state, can lead to this increase in the lymphomas. The HPV, which we now have a vaccine for, so hopefully this will become a vanishing memory, is related to the risk of cervical cancer. In patients who are immune suppressed this may increase the risk of that recurring. The Hepatitis C virus may also reactivate and lead to an increased risk of hepatitis and hepatoma. But there are also some diseases, I won't even call them cancers, that we do transplants for, where even beyond transplant the intrinsic disease leads to an increased risk of cancer. In Fanconi anemia there is an inability to repair the DNA, which may by itself lead to a risk of cancer. AML and myelodysplasia have a 4 to 8% incidence, usually within a 12 to 14-month time period after treatment. Again, treatment with alkylators, the topoisomerase inhibitors, radiation therapy, in stem cell transplantation when we give an inadequate stem cell dose that may lead to this, and use of total body radiation is associated. These are certainly not certainties, but it does contribute to the incidence. The B Cell lymphoproliferative disorders, especially when we reduce the T cell function, because they're in there fighting for us but they also can cause problems and complications such as Graft-versus-Host Disease. We're still working on trying to find the balance. Solid tumors, I mentioned skin cancer, breast cancer, especially associated with radiation, oral cancers for patients who develop dry eye or dry mouth. Highest cumulative incidence is about 6-11% at 15 years, and the highest risk is for those bone marrow transplant patients receiving therapy under age 10. It's, again, related to the use of immunosuppression, Graft-versus-Host Disease, viral reactivation, and radiation.

So what about the quality of life? We've talked a lot about the medical things, but clearly that's not all that we bring, that's not all that we are. There are a number of different quality of life studies that I'm just going to mention to you about after cancer treatment with chemotherapy and after bone marrow transplantation. A number of studies looking at patients showed that physical functioning returned to pre-transplant levels, or 75% of levels, by one year. Eighty-five percent of patients who went through stem cell transplant returned to work or school. At one year there was a modest decline in IQ by about 6 points, as it could be measured. But one to three years post usually this increased. When we look at the pediatric population, the highest risk was for those who received stem cell transplant under age 6 and especially those under age 3. This is a very important formative time and that may be where we're seeing the greatest impact. The majority of patients after transplant have very good psychological health. Thirty-five percent did show high levels of anxiety afterwards. Sixty percent said in their questionnaires that they felt vulnerable afterward. Thirty-five percent felt that they had unfulfilled needs in their love lives, suggesting a variety of different stressors in relationships with their loved ones. But, there were no differences in family and peer relationships, school performance, and self-esteem when compared with another group of patients who went through chemotherapy and not stem cell transplantation.

The Seattle study looked at 120 adult survivors of childhood transplant for leukemia. They compared them with 114 chemotherapy and 149 chemotherapy controls and 149 people who never went through cancer treatment. They found that physical dysfunction, some sort of inability to perform all of their activities, occurred in 6.8% of those with transplant versus 3% with chemo. Interestingly, there were more problems with memory for patient's who went on chemotherapy, but there was more concern for depression after bone marrow transplantation. Clearly, the transplant patients required more M.D. visits, there was more of an incidence of diabetes, and there was an increased risk of secondary cancers, 8.4% after transplant versus 2.6% with chemo versus 1.4% in those that never received treatment. But, psychosocial factors were equivalent to those that never received any treatment whatsoever.

Comparative work ability. Another study looked at 591 patient who were treated for breast, lymphoma, testicular or prostate cancers and compared them with 750+ controls. The work ability of the cancer survivors were no different than those who did not receive treatment. Physical limitations to work occurred in 26% after treatment. Those who felt that they had some sort of difficulty with cognitive ability in about 19%, but it was more common after chemotherapy, more common if people had other health issues that they were also being treated for as they went through their treatment, and less likely if people had a very strong commitment to work, and very less likely if they had a good social climate at work. So love what you do, and love the people you work with.

Family stressors. For stem cell transplantation, sibling donors often feel responsible for the complications of stem cell transplant. This is at any age.

They may have increased anxiety themselves as they approach the age of their affected sibling. They may have anniversary issues at the time of diagnosis, treatment start or end. This is true for everyone in the family. I'm sure there are those of you who know exactly what I'm talking about. Younger parents who have unresolved anxiety or depression at the time their child or they themselves go through bone marrow transplant require intervention because in those people there is a higher incidence of post traumatic stress disorder. This doesn't just happen to people who have been through combat. This happens to anyone who has had a major life-changing event. Depression is also a concern. These are things we need to be aware of. It's not just what's happening to our bodies. It's what happening with our ability to function as an entire person.

I'm going to leave these for the write-up. Long-term follow-up. It talks about all the various things that can occur. Quite frankly, these are all part of a normal long-term follow-up exam that you would have when you return to your primary care physician and to your oncologist for programs like Dr. Dunn's and programs that are being set up like the Survivors Clinic that is being developed in the Massey Cancer Center, and like the Long Term Follow Up Clinic that is being set up for bone marrow transplantation. So what I'd like to leave you with is that it is true – chemotherapy and bone marrow transplant are increasingly curing patients with otherwise fatal illnesses. It is lovely to have so many of you here to have to solve these problems, to have to address these problems, and to have to find solutions for these problems. As we increase the numbers of successful treatments we will need to address these late complications, and this is not just the oncologist's issue. This is a multidisciplinary team approach. What we're going to see is much of what we're seeing in the clinical trials at the Massey Cancer Center that, as we have a new drug, there is always a long-term follow-up component to these studies. This is a new thing. This is very exciting as well. And it's also the responsibility of places like the Massey Cancer Center program, such as the stem cell and bone marrow transplant program, to do studies, to get involved in not just treatment trials but in long-term follow-up trials so that we can identify not just issues, but also find solutions. So we're looking at preemptive monitoring and health maintenance that will allow better prevention and more effective management of long-term potential complications – and allow us to enjoy our lives fully. Thank you.