

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

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

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Living With Survival: The Childhood Cancer Survivor

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Thank you, Mary Helen, and good evening everybody. Thank you for coming. I hope I'll be able to give you some information tonight about the childhood cancer survivor.

In the beginning, few children survived their disease, so the concept of late effects really didn't exist. You have to live long enough to develop a potential late effect. But now things are looking up. We have some good news. The good news is not that 7,500 children under the age of 15 are diagnosed with cancer every year. The good news is that we are currently predicting for the child who is diagnosed currently that there is an 80% chance that that child will be a long-term survivor. It's currently estimated that in the United States there are approximately 270,000 people who have survived childhood cancer. That works out to be about 1 in 1,000 is a childhood cancer survivor. If you look at it among young adults ages 20 to 34, it's estimated that as many as 1 in 570 is actually a childhood cancer survivor.

This is all a function of our success. Back in the 1940s and 50s, almost nobody survived childhood cancer. Toward the end of the 1940s the first chemotherapeutic agent was developed. The rest, as they say, is history because it's really with the development of chemotherapy that we've made such an important contribution to survivorship in pediatric cancer. As these new drugs were developed, starting in the late 1940s and then escalating rapidly through the 1950s, 1960s and 1970s, we learned how to put the drugs together for combination chemotherapy to increase the efficacy. We started to have an

enlarging population of pediatric patients who became survivors and became the basis for our childhood long term cancer survivor studies.

Unfortunately, since that time, what we've uncovered is that there are a large variety of toxicities that affect virtually every organ system in the body that have been attributed to this therapy. We have a number of different therapeutic modalities to treat cancer. We'll be hearing about several of them from the other speakers after me but, basically, we have chemotherapy, which has made such an inroad for the treatment of childhood cancer, and we have radiation therapy, surgery, and bone marrow or stem cell transplant. Unfortunately, every one of these modalities has potential late effects.

What is the bad news? The bad news is that studies have shown that at least two-thirds of our childhood cancer survivors will have at least one late effect. One-third of them will have two or more late effects, and about one-third of these patients will have a very serious late effect. The incidence of these late effects tends to increase with age, as the patient gets further and further out from their diagnosis and treatment. Often these late effects are clinically silent for years and years and only become clinically apparent decades after the therapy has ended.

Most of the information, or a great part of the information that has become available to the pediatric oncologists concerning the childhood cancer survivor has come out of a very comprehensive study that started about twelve years ago in 1994. It's a multi-institutional study that involves about 25 institutions across the country. It's called the CCSS, or Children's Cancer Survivor Study. They have enrolled probably 13,000 to 15,000 patients who are at least five years out from their initial cancer diagnosis. They've been able to compile a lot of data and they've put together a number of publications. This is some data that has come from this CCSS study that was published in 2003 in the *Journal of the American Medical Association*. What they've found is that, if you go to the bottom of the slide, 43% of this group that they published on, which is about 9,500 young adult survivors, about 43% were found to have a moderately severe late effect. These took all different forms. Some of them were physical problems and some of them were emotional or mental problems.

Two years before that, in 2001, in the *Journal of Clinical Oncology*, another important journal for oncologists, there were two studies that were published in the same issue, back to back, and they both were looking at childhood cancer survivors. One of them was the CCSS study, but another one was actually based in Europe. Between the two studies there were almost 34,000 long-term survivors, which were defined as patients who had been diagnosed at least five years earlier with a pediatric malignancy. What was interesting about these two studies was that they found the identical increased risk of mortality for these two groups of patients. Basically, what a standard mortality ratio means, and it was 10.8, is that in these patients who were childhood cancer survivors, they had almost an eleven-fold increased risk of having some event which caused their

death. In two-thirds of the patient's the excess mortality was due to a recurrence of their initial cancer. But the group that is most interesting to me is this group which consisted of about 20% of the patients who mortality was due to either the development of a second malignancy or some other cancer-related cause. This is a pie chart looking at what caused the excess late mortality that was related to their previous treatment for childhood cancer. I think you can see that in 60% of these patients who died, it was because they had developed a secondary malignancy, a second diagnosis of a different form of cancer, not a recurrence but a totally new malignancy. In 21% it was related to cardiac or heart causes. And in about 8%, pulmonary or lung causes.

Looking specifically now at this CCSS data, they found a number of associations which seemed to be closely associated with the excess mortality. For those patients who developed a second malignancy, they found that those who developed a solid tumor, that seemed to be related to patients who had previously been irradiated because a lot of these solid tumors developed in the radiation therapy field. In some of the patients, the second malignancy took the form of a form of leukemia and that seemed to be more chemotherapy-related. These patients had been treated with two different classes of drugs – either one in the alkylator family of chemotherapy or another family of chemotherapeutic agents with this lovely word which is quite a mouthful, but I've eventually learned how to pronounce it, and it's epipodophyllotoxins. The pulmonary mortality was most closely associated with patients who previously had radiation to their thorax or chest and/or were treated with a particular chemotherapeutic agent whose name is bleomycin. The cardiac mortality was associated with patients who had been treated with another family of chemotherapeutic agents in the anthracycline family and/or had radiation to the chest.

Let's look a little more closely at some of these potentially life-threatening late effects. As I've said previously, we've seen late effects in almost every single organ system. It is really beyond the scope of a 20-minute talk to try to go over them in any kind of detail, so I've chosen to focus on the effects that have been found in these studies to be potentially life-threatening.

The first one I'm going to discuss briefly is the development of the second malignancies since 60% of the excess mortality was related to the development of another tumor. First, I'd like to briefly mention the secondary leukemias which, as I said before, mainly related to the chemotherapy that many of these patients received. There have been a number of families of chemotherapeutic agents that have been associated with the development of secondary leukemia, usually a form of myeloid leukemia or AML. The families of drugs that have been found to be associated with this development include, again, those alkylating agents, heavy metals, epipodophyllotoxins (I just love saying that, it just rolls off your tongue), and the anthracyclines. What's interesting about the development of secondary leukemia in childhood cancer survivors is that it has what's called a relatively short latency period. That's the period of time between when the treatment was actually given and when the event occurs. In this particular

instance, it tends to be a pretty short period of time between the two and is often measured in just months to a few years, and then the risk seems to dissipate. Just very briefly, the signs of leukemia may include pallor and fatigue because the patient gets quite anemic, recurrent and/or unexplained fevers and infections because of the white cell abnormalities, easy bruising and abnormal or excessive bleeding because of low platelet counts, and sometimes the patient also has fairly severe bone pain.

What about the radiation-induced second malignancies? These may take a wide variety of forms including skin cancer, soft tissue sarcomas, bone tumors, brain tumors, thyroid cancer, and breast cancer, but certainly this is not a complete list. These malignancies, as opposed to the chemotherapy-related malignancies, usually have a relatively long latency period and it often may be 20 years or more, and I'm sure Dr. Anscher will be discussing this in a lot more detail.

This is, again, some more data from the Children's Cancer Survivor Study. This is looking at the incidence of second malignancies in the patients in the study, the cumulative incidence here versus how many years from the initial diagnosis. You can see that this is a pretty steep curve that continues ever upward and never seems to plateau even 25 years out from diagnosis, although, please keep in mind that the cumulative incidence here is only 5%, but 5% at about 25 years.

Just briefly I'd like to touch on some of the other potentially life-threatening late effects. For instance, lung toxicity. Lung toxicity may be caused by exposure to a number of chemotherapeutic agents, not only Bleomycin which I mentioned before, but BCNU or CCNU are two other agents, and another one is Busulfan, and/or radiation to the chest. Symptoms of pulmonary toxicity may include exercise intolerance, shortness of breath, frequent coughing or wheezing, and frequent lung infections.

Again, just briefly, touching on some of the potential heart problems. The cardiac toxicity seen in childhood cancer survivors is mainly caused by exposure to a group of drugs called the anthracyclines. The most famous or, if you will, infamous of these agents include Doxorubicin – also called Adriamycin, or its kissing cousin Daunorubicin – and/or chest irradiation. The symptoms of cardiac toxicity may include shortness of breath, dizziness, fainting, fatigue, chest pain, swollen ankles, persistent cough or wheezing, racing heart, or an irregular heartbeat.

We know that survivors of childhood cancer face an increased risk of future health problems. These take a wide array of forms and typically show a clinically silent period for many years. The good news is that many of them have potentially modifiable outcomes. We know that they are at increased risk for second cancers, so if we're following the patients and we know they have this risk we can screen them and look for it and hope to pick up things early while they are still treatable and curable. We can try to prevent the patient from further increasing the risk of developing malignancies by trying to counsel them to lead a

healthy lifestyle. For instance, avoiding tobacco, using alcohol in moderation, using sunscreen when they're out in the sun, having a healthy lifestyle with a moderate amount of physical activity and a healthy diet. Again, health behaviors counseling is a very important part of the long-term survivor program.

We know that the health problems post-cancer are multifactorial. I just talked briefly about trying to modify some health behaviors, but there are many other things that go into determination of what types of problems and who will develop health problems after a diagnosis and treatment for a malignancy. One of the major problems we face as pediatric oncologists is that as patients get further and further out from their diagnosis they tend to come back to see us less and less often, so we have a chronic, severe problem with patients being lost to follow-up. This is some additional data from the CCSS study published in 2004 in the *Annals of Family Medicine*. It looked at the percentage of survivor visits to a cancer center. It looked at a population of almost 13,000 long-term survivors, and it looked at how many of them went back to their cancer center and had an appointment with their oncologist in the previous two years. It goes from seven years from their diagnosis out to 25 years. You can see, even at seven years, we're not doing too well. Only 30 to 40% of patients are still going back to see their oncologist. But then it gets worse and worse as the number of years out from diagnosis increases. We need to reach this population because we have new information about late effects that may be potentially important to them.

Our understanding of the risks of cancer therapy during childhood is currently evolving. What we know now, in many cases, we didn't know five or ten years ago. And what we know now may be laughable in terms of what we may know five or ten years in the future. Every survivor appears to have different needs based on his or her individual risk assessment. Most survivors are without obvious current problems, but we know that they may face an increased risk for a wide variety of health problems in the future. What we would like to develop for every cancer survivor is what we call a LIFEPLAN. It's a systematic plan for screening, surveillance, counseling, and prevention. We need to incorporate the survivor's risks based on what type of cancer they had and what kind of cancer therapy they received. We also have to take into account any particular genetic predispositions based on the patient's family history, what their lifestyle behaviors are like, and what other comorbid health conditions may coexist. This needs to be a comprehensive plan, and it really needs to be lifelong.

Just a quick, shameless plug for our Pediatric Survivorship Clinic, which has been up and running as of next month for two years. I run it, along with one of my devoted nurse practitioners, Anne Mauck. We meet almost every Wednesday, but basically we will accommodate most any schedule at the Nelson Clinic, at the corner of 11th and Marshall. To qualify to attend the Survivorship Clinic you need to be a minimum of five years out from your diagnosis and at least two years off therapy. Right now we are not imposing any upward age limit, even though we're pediatricians. We will see adult survivors of childhood cancer, and actually the oldest survivor that we have seen was 40 years old.

Appointments can be made at the phone number 828-9300. This is a book that we hand out to all our survivors at their first visit. We review their chart. We go over all of their treatment. We put a written summary together both for the chart and at the back of this book, where we have a little folder that's perforated and can be torn out and we call it a Treatment Passport. It sounds a little hokey but, just like a passport that you have to carry with you as you go from country to country, we would like as you travel through life that you can carry this treatment passport with you and share it with your family and share it with your new physicians as you, again, travel through life. This is an excellent book which gives a lot of information to our survivors, and we have a lot of written handouts that are put together and tailored for the patient and what their treatment was and what we deem as their potential risks. We try to arm our patients with as much information as possible.

Thank you for your attention.