

FEATURE STORY

Treatment Aftershocks

BY RABIYA S. TUMA, PHD

Survivors guided through territory of long-term and late effects.

Vladimir Vukicevic was 5 years old when his family left their native Belgrade in the former Yugoslavia to come to Memorial Sloan-Kettering Cancer Center in New York, where the young boy would be treated for Ewing's sarcoma, a bone cancer that most commonly afflicts children. After chemotherapy and a bone graft in his right femur, all looked good for a few years. But at one of his twice-yearly checkups, Vukicevic's doctor found that he had developed leukemia, most likely a result of the chemotherapy used to treat the original cancer. Vukicevic received more chemotherapy and a bone marrow transplant, and the now 17-year-old business and management student at New York University considers himself cancer free.

For Vukicevic and other survivors of pediatric or adult cancers, surviving is only the first part of the battle. After completing therapy, survivors can continue to experience the side effects of therapy or develop new problems associated with treatment. Like most survivors, Vukicevic still sees his oncologist and endocrinologist every six months for screening and physicals. He takes a synthetic thyroid hormone pill each day because his thyroid stopped functioning normally about six months after treatment. "That is a daily reminder of what I went through," he says. "It has become a habit, but every once in a while I realize why I am taking it."

Long-lasting effects of cancer therapies, such as thyroid dysfunction, are not at all uncommon, says Smita Bhatia, MD, associate director of the City of Hope Comprehensive Cancer Center in California, who specializes in long-term effects of therapy for pediatric and adult survivors.

The timing of onset of such complications can vary widely. Some problems, such as fatigue, can begin during therapy and may continue indefinitely, though the duration and severity differs greatly between individuals. Conditions that start during therapy and persist for months or years, sometimes referred to as long-term effects, differ from those that start well after therapy has been completed, which are considered late effects.

Thyroid dysfunction can start during therapy, shortly after therapy or years later. Researchers know that some late effects of treatment, such as second cancers, tend to occur within a specific period of time. Leukemias and other blood cancers caused by some chemotherapeutic agents tend to develop within several years after treatment—as was the case for Vukicevic. In contrast, the risk of solid cancers, which are caused by radiation, continues to increase even beyond 10

years after therapy. Such long-lasting risk illustrates the need for new models of survivorship care and research for the growing number of cancer survivors in the United States, issues that are beginning to be addressed at the growing number of survivorship centers and clinics around the country.



Vladimir Vukicevic, a college student in New York City, survived a second cancer that resulted from previous treatment. Photo by Andrew Schwartz.

Long-Term Survivorship

While both adult and pediatric cancer survivors experience post-therapy effects, more is known about survivors of pediatric cancer because long-term survival became common in pediatric cancers earlier. Data from the Childhood Cancer Survivor Study shows that out of a group of more than 10,000 survivors, two-thirds had at least one health condition and a third had multiple problems. Moreover, pediatric cancer survivors were four times more likely to have a severe or life-threatening health condition than were their siblings.

Charles Sklar, MD, director of the pediatric Long Term Follow-Up Program at Sloan-Kettering, says the issue of research in adults is complicated by the fact that as people age normally, they develop a lot of other medical problems, or comorbidities. “So it is not completely clear which ones might be due to the treatment, which ones might be due to aging and which ones may be an interaction between the two.” Researchers are just beginning to look systematically at the physical and psychological issues of being a survivor of adult cancer.

For cancers, such as Hodgkin’s disease and brain cancer, where the disease and the treatments are similar in pediatric and adult populations, the complications also tend to be similar, though children are more sensitive to some treatments because their bodies are still developing. One of the most common effects for children who receive radiation to the brain is cognitive problems, such as learning disabilities. While researchers work on ways to minimize or even repair such damage, Dr. Sklar says early diagnosis is critical for affected children.

However, most cancers only occur in one age group or the other, and treatment-related effects are limited to that population. For instance, lymphedema occurs when the lymph nodes are damaged or removed during treatment, leading to swelling and fluid retention. Since no pediatric cancer requires routine lymph node removal, pediatric cancer survivors rarely suffer this side effect.

Because risk varies depending on the therapy used, Dr. Bhatia and others have put together a comprehensive list of treatments and the long-term complications associated with them, including heart damage, bone loss and infertility. The information can be found at www.survivorshipguidelines.org. To help survivors understand the implications of the data, her team included specific recommendations about who should undergo what type of screening and at what frequency, based on treatment history. “These guidelines are for childhood cancer

survivors, but they are very applicable to adult cancer survivors also,” says Dr. Bhatia.

Dr. Sklar recommends survivors see a specialist if at all possible because the impact of cancer therapy is ongoing. Specialists can be found at survivorship clinics, which are often found at major cancer centers and at some large hospitals. As survivorship issues gain more attention, more clinics are expected to open around the country. Patients have follow-up appointments with oncologists, as well as access to family practitioners, social workers who can help with employment or education, and psychologists or psychiatrists to help with emotional issues.

“Survivor clinics help patients get access to programs they wouldn’t otherwise have,” says Michael Irwin, MD, a researcher at UCLA’s Jonsson Comprehensive Cancer Center. The clinics also provide a way to integrate treatment and research.

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—Vladimir Vukicevic

Dr. Irwin recently teamed up with the cancer survivorship clinic at UCLA to learn why as many as one-third of breast cancer survivors suffer from severe fatigue even years after therapy. They found that women with chronic fatigue had overly active immune systems. While it is understood that the immune system is activated to fight the disease during treatment for breast cancer, Dr. Irwin hypothesizes that it is not effectively turned off after treatment for some reason. The team is now looking for ways to treat the underlying biochemical problem using behavioral approaches like tai chi and yoga, which help slow immune system activity according to preliminary evidence. “A medical approach with drugs could work, but many survivors do not want to take more pills or shots,” says Dr. Irwin. His team is now researching possible correlations between fatigue and activated immune systems in other malignancies, such as prostate cancer.

In addition to looking for ways to treat lasting effects, researchers hope newer therapies will provoke fewer problems. Molecularly targeted therapies, such as Gleevec® (imatinib) and Herceptin® (trastuzumab), are designed to treat the disease without damaging healthy tissues—and that should mean fewer long-term and late side effects. Clinical researchers are also looking for ways to modify existing therapies to limit the problems they cause. Such changes include using narrower fields of radiation and lower doses of chemotherapy. The American Society of Clinical Oncology has even established a Survivorship Task Force that will develop a template for physicians that details possible long-term and late effects of different treatments and provides guidance on monitoring for disease recurrence.

Not everything that comes from cancer is negative. When Dr. Bhatia and colleagues looked at survivors' quality of life they found "their spiritual well-being is amazing."

For Grace Butler, PhD, a truer statement couldn't be made. She was diagnosed with stage 3 colorectal cancer in 1999. During treatment, she told one of her friends, "I will not succumb to cancer."

"That was more than a statement," says Dr. Butler. "It was a position, an outlook, an expectation: This is not going to take me down."

Prior to her diagnosis, Dr. Butler was a professor of education at the University of Houston, but things changed dramatically after her diagnosis. "One day I was sitting at my desk doing what I was supposed to be doing—that was a Wednesday. On Thursday I was admitted into the hospital. Tuesday I had a diagnosis. I never returned to that desk. It was a defining moment in my life."

As she started to become more aware of cancer and how it affects people, particularly those who cannot afford health insurance or who do not have access to care, she did something about it. After completing her treatment, she started a nonprofit organization called Hope Through Grace (www.hopethroughgrace.org) that provides prevention education workshops and other services for the community.

Though she suffers from chronic pain and fatigue, "I can see so many blessings that have come to me as a consequence of cancer. Now don't misunderstand, I would never ask, 'Please let me have cancer,' but the long-term effect for me has enabled me to help others. That is what cancer has done for me. Not to me, but for me."