Healing the cancer, hurting the heart

Working in a new medical field, a handful of experts have realized that chemotherapy and radiation treatment for oncology patients may harm cardiac health

Judy Siegel-Itzkovich interviews an Israeli pioneer in the field

(TNS)

Over a decade ago, cancer overtook heart disease as the most common cause of death in the Western world. But who would have thought that chemotherapy and/or radiation treatment for malignant tumors may actually cause cardiovascular disease in cancer survivors?

It can, and a handful of medical centers abroad have begun to realize the connection. But it has only recently reached the attention of some cardiologists and oncologists here – and medical schools, hospitals and physicians are hardly aware of it.

Dr. Zaza Iakobishvili, director of emergency cardiology services at the Rabin Medical Center-Beilinson Campus in Petah Tikva is one of the early birds. He recently opened the country's only dedicated cardio-oncology clinic and is receiving cancer patients once a week with the aim of following up, preventing and treating cardiovascular complications resulting from their cancer treatment.

He was born in Kutaisi in Georgia of the former Soviet Union, an ancient city of the same age as Jerusalem and now Georgia's second-largest city. Until the 1970s, before the mass exodus of Soviet Jews, there were as many as 100,000 living there.

"Now there are only 5,000 Jews," Iakobishvili told *The Jerusalem Post* in an interview. "I came in 1996 to live in Bat Yam with my wife and two children, who were small then. My wife is an economist, my 25-year-old daughter is a biologist and my son, 23, is a student of biomedical engineering."

When they arrived, Zaza was also a cardiologist; he had received his medical degree in 1988 from the Tbilisi State Medical University and completed his postdoctoral training at the Tbilisi Institute of Human Physiology.

Not knowing Hebrew except for his vague recall of the prayers of his childhood, Iakobishvili completed a residency in internal medicine at Rabin Medical Center-Hasharon Campus and received board certification in the specialty after successful completion of the qualifying examinations. Later, in 2001, he successfully passed board certification in cardiology and worked in the cardiac intensive care unit from until 2009, when he was appointed to direct Beilinson's emergency cardiology services. From 2008 to 2010, he was secretary of the National Cardiology Board examination committee, and was recently elected chairman of the Israel Heart Society's working group on acute cardiac care.

His main fields of interest include cardiogenic shock (when the heart has been so damaged that it can't supply enough blood to the body's organs), acute coronary syndromes and acute heart failure, diabetes treatment in cardiac patients and heart biomarkers. Now fully fluent in Hebrew, the cardiologist teaches at Tel Aviv University's Sackler Faculty of Medicine and has been repeatedly named among its best teachers.

DR. ZAZA IAKOBISHVILI (Courtesy)

'WE NOTICED in my unit that many cancer patients suffered from cardiac problems. They weren't huge numbers, but we were sure there was an increase in the admission of oncology patients to the acute cardiac care facility. Widespread perception at the end of Nineties was that most cancer patients would die anyway, so there was no reason or time to treat their heart problems, and on the opposite [side] oncologists were scared of heart problems in their patients and avoided the use of the most effective drugs (frequently but not uniformly with more cardiotoxic potential)."

The phenomenon piqued his interest, so he began to read up on it. "I also contacted what they called 'cardio-oncology units' and spent a few weeks at a large 400-bed center in Milan where there is a facility for treatment of heart problems in cancer patients," he said.

Major US centers with such a clinic are the Mayo Clinic, the MD Anderson Cancer Center, the Memorial Sloan Kettering Cancer Center, the Dana-Farber Cancer Institute and the Brigham and Women's Hospital.

The American Cancer Society also knows a lot about this subject; Israel Cancer Association director-general Miri Ziv enthusiastically endorses activity in the field here.

Iakobishvili, encouraged by the support of Prof. Ran Kornowski, chairman of the Rabin Medical Center's cardiology department, asked director-general Dr. Eyran Halpern for permission to open a once-weekly cardio-oncology clinic at Beilinson, and when Halpern agreed, he established it, over a year ago.

Founding this clinic in the Rabin Medical Center was a very natural move since the largest Israeli cancer center, Davidoff Comprehensive Cancer Center, is part of Rabin Medical Center. A close cooperation was established with the oncology department (director Prof. Baruch Brenner) and hematology department (director Prof. Pia Raanani), making the clinic a success story. The "Patient Centered Approach" is thoroughly implemented in the clinic, allowing patients with "double trouble" the best care.

Last month, the cardiologist and his colleagues from RMC hosted and headed the Israel's first-ever cardio-oncology conference at the Tel Aviv Hilton, attended by 250 people, a third of them oncologists, a third cardiologists and the rest hematologists (experts in blood diseases, including leukemia and lymphomas).

"Five speakers, top experts in the field, came from abroad. It was very successful. We hope to make it an annual event. We have planted the first seeds," said Iakobishvili.

The Israel Medical Association hasn't yet recognized or even discussed cardio-oncology as a sub-specialty. Neither has the Health Ministry. But Iakobishvili is participating in the preparation of guidelines for training that will be published soon.

"We are also preparing an article for IMAJ [the English-language IMA journal], and we will write about it in *Harefuah*, the IMA's Hebrew-language journal, which will dedicate a whole issue to the Rabin Medical Center."

The survival rate among cancer patients in the US and other developed countries has grown in the past quarter of a century. Compared to a five-year survival rate of 50 percent in the mid-Seventies, it has risen nearly to around 70% in recent years, thanks to more effective and precise chemotherapy and radiotherapy. But many of these treatments are cardiotoxic, meaning that they can cause collateral damage to the heart and blood vessels, causing either damage to the heart muscle or disrupting the electrical activity in the organ. This effect can not only shorten lives of recovering cancer patients but also lower their quality of life, said Iakobishvili.

HE EXPLAINED that among the cytotoxic effects of chemotherapy in oncology patients are ischemia (in which the heart lacks oxygen, causing the muscle cells to die); interference with heart pumping; arrhythmia (irregular beats) and pericarditis (inflammation if the fibrous tissue that covers the heart). Not only chemo drugs are to blame; so is radiation, especially when administered to the chest, which can cause disease to the heart valves, clogged coronary arteries and injury to the pericardium. When patients undergo both chemotherapy and radiation treatment, said the Beilinson cardiologist, it can compound the problem.

"There are some very good off-the-shelf drugs for chronic myeloid leukemia (CML), as well as other cancers, that are said to increase the risk of heart disease and stroke, but by careful patient selection and risk factor management probably their use will be safer. We are planning a study to elaborate on the cardio-vascular damage mechanisms of some of these medications."

About 10% to 20% of chemotherapy drugs cause such serious heart complications that doctors decide to stop administering them. When studying chemotherapy agents, Iakobishvili found that they are classified as Type 1 and Type 2 according to their effect on the heart. The first category includes the anthracycline drugs such as doxorubicin, idarubicin, cyclophosphamide, docetaxel and epirubicin, which have been used during the past half-century. Iakobishvili said the damage they cause usually depends on the dosage and when they are administered. Unfortunately, their effects – which include dysfunction of the heart's left ventricle and congestive heart failure – are irreversible. The heart damage of anthracyclines is usually worse in older cancer patients and those who have already suffered heart disease.

Among the Type 2 agents are kinase inhibitors. These are more modern anti-cancer agents, including imatinib, bevacizumab, trastuzumab, lapatinib and sunitinib, and their cardiotoxicity is usually not related to the dosage; if they cause harm to the heart, it is often reversible, said Iakobishvili. Besides causing heart damage, however, they can also induce high blood pressure.

Women with certain kinds of breast cancer may be treated with trastuzumab (commercially known as Herceptin), a monoclonal that has turned into a breakthrough drug, and if it causes heart damage, in about 80% of cases it is reversible. But Herceptin is usually combined with anthracycline chemotherapy, whose cardiotox effect is usually permanent. Women survivors of breast cancer are frequent patients to Iakobishvili's clinic because of this.

He noted that there is no Israeli database listing chemotherapeutic agents and their cardiotoxic effects, so without local research, people interested in the sub-specialty will have to depend on foreign material. Specialist centers abroad are currently at a more advanced level in terms of education, seminars, treatment and guidelines than Beilinson, but Iakobishvili intends to catch up.

"This is such a new field that it takes a lot of effort to make people understand. There is no uniformity in the knowledge of the effects of chemotherapy and radiation on the heart," the cardiologist stressed. "Childhood cancer survivors undergo radiation as children, and in their 30s, they may reach the hospital with a heart attack."

As a result, the new Beilinson clinic will actually seek out cancer patients who have been cured or are in a relapse and check them for early signs of heart disease.

"Radiation today is much more precise, so there is less damage. But it still can cause harm. The more we learn about specific chemotherapy drugs and their effects on the heart, the better off patients will be. Obviously, one can't stop giving anti-cancer treatment to prevent heart disease; treating the cancer is the top priority."

ASKED WHETHER cancer patients' cardiovascular health could benefit from ordinary measures to prevent heart disease in healthy people or reduce risk in heart patients, Iakobishvili answered in the affirmative. "Exercise, the proper diet, not smoking and medications can certainly reduce the risk."

His team are not afraid to approach cancer patients to tell them about possible harmful effects on their heart of cancer treatments.

"Most take is well and ask questions, but there are some who say they're overwhelmed by their oncology treatments and don't want to hear of it. If so, it's my job to try to persuade them."

Advanced scanning techniques such as strain-imaging echocardiography and MRI can help in diagnosing heart disease in cancer patients, he continued.

"One can see the heart contracting abnormally, and this is a sign of cardiotoxicity. But more research still needs to be done."

So far, the health funds have not made a fuss about paying for visits, especially Clalit Health Services, which owns Beilinson.

"We hope to gradually increase the number of days the clinic is open as patients and doctors become more aware of what we do. I myself spend most of my time in emergency cardiology. In any case, we are trying to raise a new generation of oncologists and cardiologists who are aware of the effects of treatment of cancer care on the heart."

When questioned on what his new Monday clinic has meant to patients, he concluded with a smile: "I can say that in the last year, 80% of our clinic patients are healthier than when they arrived. We feel we're making a difference."

Not all neutrophils are created equal in fighting cancer

HEALTH SCAN

• By JUDY SIEGEL-ITZKOVICH

The most common form of white blood cells – called neutrophils – contain many different subtypes, of which some fight the development of cancer and others promote its progression. New Hebrew University research could help pave the way to new therapies that fight cancer by increasing anti-tumor neutrophils while limiting pro-tumor neutrophils.

Traditionally, cancer research has focused on trying to identify aspects of cancer development that can be exploited therapeutically with chemotherapy and radiation. In the last decade, new approaches to cancer have involved activating the immune system against cancer cells without harming healthy tissue, which has proven effective in a limited range of patients.

However, in recent years it became clear that in addition to the cancer cells themselves, healthy cells surrounding a tumor play a critical role in promoting cancer development. These cells, which provide a supportive environment that promotes tumor growth and allows it to spread, are potential targets for new cancer therapies.

The role of neutrophils, which comprise between half to 70 percent of all white blood cells, remains controversial. While neutrophils are traditionally associated with inflammation and fighting infections, accumulating data suggest they also play an important role in tumor biology.

In a just-published study in the journal *Cell Reports*, Dr. Zvika Granot and Dr. Zvi Fridlender scientists working with mouse tumors and human blood samples challenge the concept that mature neutrophils are limited in their ability to change and take on new characteristics. They also show that in contrast to current perceptions, neutrophils are not a homogeneous population of cells but rather consist of multiple subtypes.

The researchers found that while some neutrophils have anti-tumor properties, others in fact promote tumor progression. They also showed that in early stages of the disease, tumor-limiting neutrophils prevail. However, as cancer progresses, the tumor-promoting neutrophil subpopulation that promotes tumor growth outcompete the tumor-limiting neutrophil subpopulation, and the overall neutrophil contribution becomes tumor-promoting.

"The novel distinction between harmful and beneficial neutrophils opens up new diagnostic and therapeutic opportunities," Granot said. "We are currently evaluating the effects of boosting the helpful anti-tumor neutrophil population, while limiting the tumor-promoting neutrophil population, on progression of the disease. If successful, this therapeutic strategy may take us closer to developing effective new therapies for cancer."

SMOKING AND PROSTATE CANCER

Among patients with prostate cancer, those who smoke have increased risks of experiencing side effects from treatment and of developing recurrences or even dying from prostate cancer. The findings, just published in *BJU International*, suggest that smoking may negatively affect the health outcomes of patients with prostate cancer contribute to complications related to their care.

Several studies have demonstrated links between cigarette smoking and prostate cancer. To better understand the influence of smoking on prostate cancer progression and treatment, radiation oncology Prof. Michael Zelefsky of New York's Memorial Sloan Kettering Cancer and colleagues studied 2,358 patients who underwent external beam radiotherapy for prostate cancer between 1988 and 2005. Of these, 2,156 had a history of smoking. Patients were classified as never smokers, current smokers, former smokers, and current smoking unknown.

Over a median follow-up of nearly eight years, patients who were current smokers had a 40% increased risk of cancer relapse, as well as more than double the risk of cancer spread and cancer-related death, compared with patients who were never smokers. In addition, current and former smokers had a higher likelihood of experiencing side effects such as urinary toxicity that were related to radiotherapy. Examples of urinary toxicity include urinary retention, urinary incontinence and bladder hemorrhage.

"Less optimal tumor control outcomes among smokers could possibly be explained by the influence of less oxygen concentration within the treated tumors among smokers, which is known to lead to less sensitivity of the cells being killed off by radiation treatments," Zelefsky noted. "Our findings point to the importance of physicians counseling their patients regarding the potential harms of smoking interfering with the efficacy of therapies and for increased risks of side effects."

JERUSALEM NEONATOLOGIST NAMED JOURNAL EDITOR

Politics sometimes thwarts capable Israelis from getting international recognition and positions – even in the field of medical research. But fortunately, highly skilled doctors can be appointed editors of foreign medical journals; the latest case in point is Prof. Francis Mimouni, chief of neonatology at Jerusalem's Shaare Zedek Medical Center, who has just been named editor of the prestigious *Journal of Perinatology*, part of the *Nature* group and the official journal of American perinatologists. The articles deal with clinical, professional, political, administrative and educational aspects of the field, and the scope of the journal reflects the multidisciplinary nature of the subject, including maternal and fetal medicine, the neonatal period and the follow-up of the infant and child.

"It is a great honor, especially at a time when [Israel's] status in the world is not outstanding. Of all the 30 editorial board members, only two are not American residents," said Mimouni.

The journal has the highest "impact factor" (measured by how often it is quoted by experts) in this field. Recently, a textbook for medical students co-edited by Mimouni on pharmacology and nutrition of newborns, including premature babies, was published. "We noticed that there as no medical textbook that presented in a systematic way the development process of drugs [in the field.] The new book presents all the phases of development, from experimentation until the final approval by the authorities, while surveying the barriers and regulation," said Mimoui. "The behavior of drugs in the body of a premie is different than that of adults, and there was a need to concentrate all accumulated knowledge in one volume and present it to professionals."

One of the articles was written by Prof. Cathy Hammerman and colleagues on the use of paracetamol to close the ductus (blood vessels in the chest) in newborns as a substitute for open-heart surgery, while Mimouni write about the development of baby formulas for premature infants.