



“NOT LONG AGO, OUR LOCAL NEWSPAPER HAD AN ARTICLE ABOUT A NEW TREATMENT FOR BLADDER CANCER. . . . THE ‘NEW TREATMENT’ IS WHAT I WAS GIVEN AT MEMORIAL YEARS AGO.”

—JOSEPH DILEO

A Matter of Time

Joseph DiLeo, 67, of Roslyn, New York, was in his mid-40s in 1983 — a husband, a father of three young children, and a high school history teacher — when his life took a devastating turn.

He was diagnosed with advanced bladder cancer. The disease had spread beyond the bladder to nearby lymph nodes and the prostate gland and was considered inoperable. However, much to Mr. DiLeo’s good fortune, Alan Yagoda, an international expert on urologic cancers and then Chief of MSKCC’s Solid Tumor Service, had just developed a new chemotherapy regimen, known as M-VAC — for the drugs methotrexate, vinblastine, Adriamycin (doxorubicin), and cisplatin. Mr. DiLeo was offered treatment with the new course of therapy.

“It was during the last year of my MSKCC fellowship in 1983 that Dr. Yagoda came up with the M-VAC regimen,” says Howard I. Scher, who is now Chief of MSKCC’s Genitourinary Oncology Service. Dr. Scher joined the staff in June of that year and has been Mr. DiLeo’s physician ever since. (Dr. Yagoda joined the College of Physicians and Surgeons of Columbia University in 1991; he died in 1995.)

Mr. DiLeo had what Dr. Scher characterizes as “a major response” to the M-VAC regimen, but the decision was made to remove his bladder anyway. “It was one of the first times we used what is now a paradigm for the treatment of bladder cancer,” says Dr. Scher, “which is to take the chemotherapy as far as you can, and then do an operation to remove residual disease.”

Recalling the diagnosis, Mr. DiLeo says, “I was told I had a Grade 4 tumor,

which is the worst. My children were young teenagers. So I said, 'I'm going to bite the bullet and do whatever I have to do.'

MSKCC urologic surgeon Pramod C. Sogani says, "If you go by the statistics, Mr. DiLeo had a five to ten percent chance of surviving two years, at best. So we said, 'Let's combine everything to see if we can improve survival.' We shrank the tumor through chemotherapy, hit it with radiation, and I operated to remove it." Dr. Sogani removed Mr. DiLeo's bladder, prostate gland, and pelvic lymph nodes and constructed a urinary diversion using an ileal conduit. The procedure

involved taking a six-inch segment of Mr. DiLeo's small intestine to form the conduit, attaching it to the ureters (which drain urine from the kidneys), and then connecting one end of the conduit to an external opening about the size of a nickel in his abdomen. Mr. DiLeo wears an external bag that collects his urine.

However, 20 years have brought many innovations. "Had Mr. DiLeo been diagnosed today, we would do the same

surgery, removing the bladder, prostate, and lymph nodes, but we would consider a different form of diversion," says Dr. Sogani. "Instead of giving him an ileal conduit, we would consider giving him a continent urinary diversion." Two main procedures are used to achieve this type of diversion. A neobladder (internal bladder) can be created using a section of small intestine so that a patient may continue to urinate through the urethra. If the neobladder cannot be hooked into the urethra (usually because it has been removed), then surgeons can create a small opening, often placed in or below the navel and easily covered with a Band-Aid®. Patients then catheterize themselves (drain their urine) several times a day.

But Joseph DiLeo still had a long road to travel. In 1988, his disease recurred in his pelvic lymph nodes and he began another cycle of four courses of M-VAC. "This time, the tumor didn't respond completely to M-VAC," says Dr. Scher, "although there was shrinkage." Meanwhile, life went on. Mr. DiLeo would check into Memorial Hospital on a Friday for his chemotherapy and would return to teaching and his family on the following Monday. "I was always working," says Mr. DiLeo. "That, and my wife and children, kept me going." Again, Dr. Scher comments: "If he were to be treated today, Mr. DiLeo would receive a less toxic regimen and would be treated as an outpatient. We have improved anti-emetics — so he wouldn't experience the same degree of nausea — and also Procrit® [erythropoietin, a human hormone made by recombinant DNA methods, given to stimulate the bone marrow's production of red blood cells] — so he would not become anemic."

Then, in 1996, Mr. DiLeo had another recurrence. "When he recurred, the chemotherapy options were limited," says Dr. Scher. "But in the intervening years, we had learned that the target of a monoclonal antibody called MDX-447

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— DAVID PFISTER, *medical oncologist*

HOWARD SCHER (RIGHT), Chief of MSKCC's Genitourinary Oncology Service, has been treating Joseph DiLeo since 1983. When Mr. DiLeo had a second recurrence of bladder cancer in 1996, medical oncologist **DAVID PFISTER** (LEFT) treated him in a clinical trial with a targeted therapy.





Surgeon **PRAMOD SOGANI** operated on Mr. DiLeo's advanced bladder cancer in 1983.

was present on the surface of tumor cells of Mr. DiLeo's type of cancer." Dr. Scher referred Mr. DiLeo to MSKCC medical oncologist David G. Pfister, who specializes in the treatment of cancers of the head and neck as well as genitourinary cancers. Dr. Pfister was then the principal investigator in a phase I clinical trial of MDX-447. Even as recently as 1996, trials of such targeted therapies were still in their infancy. MDX-447 is a bispecific antibody. One branch of the drug binds to epidermal growth factor receptor, a protein on the surface of many tumor cells that normally regulates cell growth. A second branch binds to immune cells, including white blood cells called granulocytes that can be active against cancer. In the trial in which Mr. DiLeo was enrolled, administration of MDX-447, alone or combined with granulocyte colony-stimulating factor (G-CSF), was evaluated. G-CSF, developed at MSKCC in the 1980s, is another hormone made by recombinant DNA techniques, used to stimulate the production of infection-fighting white blood cells. Mr. DiLeo was in the group that received MDX-447 plus G-CSF. The theory was that adding G-CSF to the regimen would boost the population of cancer-fighting granulocytes available to the MDX-447, possibly improving the antibody's effectiveness. Joseph DiLeo has been free of disease since 1996.

"The durability of Mr. DiLeo's response to his treatment is exceptional," Dr. Pfister says. "Most patients in the trial evaluating MDX-447 did not experience the same results. It may be that the antibody was particularly well matched to the make-up of his tumor, a concept investigators increasingly explore as we use our growing understanding of cancer biology to further the development of targeted therapies. Studies like the one in which Mr. DiLeo participated yield information that support future research — and these incremental steps add up to larger advances," Dr. Pfister says.

According to the National Cancer Institute, the chance of getting bladder cancer goes up as people age. In treating older patients for cancer, Dr. Scher explains, "a person's general health, his or her physiologic health, is a more important consideration than age." In the late 1980s, Dr. Scher and MSKCC colleagues did an analysis of prognostic factors in the treatment of prostate cancer. "Age actually came out the opposite of what you would expect," he says. "Older patients did better. Treatment options for older people with cancer should not be limited on the basis of age." [To read more about MSKCC's research efforts in cancer and aging, see the sidebar on the next page.]

"Not long ago, our local newspaper had an article about a new treatment for bladder cancer," Joseph DiLeo remarks. "The 'new treatment' is what I was given at Memorial years ago. I showed it to my wife, Brenda, and said, 'Look at this. I've had this.'" Mr. DiLeo smiles. "I'm proud to have been a part of the changes that have taken place. I'm extremely grateful to Dr. Scher, who has been my advocate for two decades and has given me every opportunity possible in the treatment of my cancer, and to Drs. Sogani and Pfister, who also helped me to survive this disease."

Cancer and Aging: A New MSKCC Program

According to the National Institutes of Health (NIH), cancer death rates are highest for people 65 years of age or older. Indeed, at a 2001 joint National Institute of Aging (NIA)/National Cancer Institute (NCI) workshop, participants noted that people 65 or older are at the highest risk for cancer. For all cancers combined, people 65 or older have an incidence ten times greater than the rate for those younger than 65. And the cancer mortality rate for older patients is 16 times greater than the rate for younger patients. Yet these patients are underrepresented in clinical trials and are referred less frequently to oncologists by their primary care physicians than younger patients with similar disease. Meanwhile, studies suggest that older patients do benefit from treatment, in some cases as much as younger patients.

There are signs that the tide is turning. In 2003, the subject received special coverage at the annual meeting of the American Society of Clinical

Oncology (ASCO). Member physicians recommended that older patients be referred to cancer specialists more often and that they have greater representation in future clinical trials. They also recommended further study to understand the barriers that may prevent older people from receiving treatment and participating in trials.

As part of the new initiative to accelerate research at the interface of cancer and aging, MSKCC was recently one of eight cancer centers to receive five-year grants from the NCI and the NIA, both parts of the NIH, to develop a formal cancer and aging program. "The purpose of this grant is to foster clinical and basic science research into the problems of cancer and aging, so we can better understand why cancer is more frequent as we age," says George J. Bosl, Chairman of MSKCC's Department of Medicine and principal investigator for the grant. "We want to learn more about how cancer in an older patient differs from the same cancer in a younger

patient and how we can better treat older patients."

MSKCC will focus on four major areas related to cancer in older patients: the medical effects of treatment and psychosocial issues (which can range from depression and treatment-associated fatigue to fear of disease recurrence and end-of-life concerns); the kinds of care older cancer patients receive, including possible age biases in cancer screening, detection, and treatment; treatment effectiveness and older patients' ability to tolerate treatment; and the biology of aging and cancer. The initial grant will allow MSKCC to create the infrastructure necessary to carry out the program. "In creating this infrastructure, we can ensure that research into cancer will take into account issues of aging throughout the Center — from patient care to basic science research," Dr. Bosl says.

In addition, the grant funding will be used to establish training programs for Center physicians at all levels to create a focus of "geriatric thinking" in MSKCC's clinical research efforts and to recruit geriatric specialists — "both clinicians at the bedside and scientists at the bench," says Dr. Bosl. The program will also include collaborations with the Division of Geriatrics at NewYork-Presbyterian Hospital and Weill Cornell Medical Center and the Cornell Center for Aging Research and Clinical Care.

GEORGE BOSL, Chairman of the Department of Medicine, is the principal investigator of a grant MSKCC received supporting clinical and basic science research into the problems of cancer and aging.

