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**-Web Exclusive-
The Biology of Cancer
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The Age Factor

By Charlotte Huff

The tumor in Jean Caldwell's breast measured 4 centimeters. And that wasn't the only bad news. First, the Wisconsin grandmother underwent a lumpectomy last summer. Then, when further tests revealed the cancer had spread to several lymph nodes, the surgeon removed nearly two dozen, along with her left breast.

Like any case of stage 2 breast cancer, the treatment options were complex. But Caldwell faced another reality—her age: 76. James Stewart, MD, her oncologist, met with Caldwell and her children several times as they discussed the relative risks of various chemotherapy regimens, including potential heart problems. Caldwell didn't waver. With three children and four grandchildren in her life, she didn't want to hedge her bets.

"I wanted to be as aggressive as I could, because I want to be cured and I want to live," she recounts. "I said to my doctor, 'I want to do everything I can.' He said he would go for the cure."

Traditionally, cancer has been associated with later life. More than half—56 percent—of all diagnoses are in Americans 65 and older, according to the National Cancer Institute's Surveillance, Epidemiology, and End Results, or SEER, data. The median age at diagnosis is 67, but demographic trends, led by the Baby Boomers, will soon boost the sheer number of older cancer patients dramatically. According to one study's projections, the number of newly diagnosed Americans age 75 and older could number nearly 1.1 million in 2050 compared with an estimated 389,000 in 2000.

That surge in patients, physicians say, will likely outpace the knowledge necessary to treat a very complex and diverse patient population. For every elderly cancer patient who struggles to live independently, another may hold down a job and play tennis three times a week. Diagnosis and treatment can be delayed or complicated by other medical conditions. Meanwhile, most chemotherapy and other research trials generally include only the fittest of seniors, if they're enrolled at all. Just 32 percent of participants in late-phase clinical trials are age 65 and older, according to a study published in 2003 in the *Journal of Clinical Oncology*.

Within the past five years, more researchers have strived to include older patients, says William Ershler, MD, senior investigator in the clinical research branch at the National Institute on Aging. Several groups, including the International Society of Geriatric Oncology and the Geriatric Oncology Consortium, are working to boost research and physician training, he says. In 2003, the NCI and the NIA jointly sponsored a five-year, \$25 million grant program focused on cancer and aging issues, including treatment, side effects, pain relief and psychological stresses, among others. Eight cancer centers received awards under the program and are currently conducting research in these areas.

Still, Dr. Ershler believes there's room for improvement. "There is a bias I have been fighting against treating older people," he says. "I think many tumor types

are very responsive to treatment. And, for some arbitrary reason, they are not offered to older people. It oftentimes comes from the families of the patient. It oftentimes comes from the nursing staff, who says, 'You're going to do what to whom?'"

In Dr. Ershler's experience, "Almost invariably, the patient says, 'I want to be treated aggressively.'"

Age and Cancer

For many of the common cancers, the development of a tumor takes considerable time, dependent upon a series of often unrelated events on the cellular level, Dr. Ershler says. Nearly 71 percent of colon cancers are diagnosed in Americans age 65 and older, according to SEER data. So are 68 percent of lung malignancies and 64 percent of prostate.

A number of cellular influences may be involved, researchers say. Over the course of years, genetic and environmental toxins, such as tobacco carcinogens, can cause DNA-damaging effects on cells. Meanwhile, the body's ability to repair damaged cells appears to decline with advancing age, Dr. Ershler says.

At the same time, the aging tissue around those damaged cells appears to play a role, creating a more conducive environment in which malignancies can grow, says Harvey Cohen, MD, director of the Center for the Study of Aging and Human Development at Duke University Medical Center. As cells age and stop dividing, it's speculated that they develop a microenvironment that fosters cancer's development, he says.

Another potential contributory factor, researchers say, is the declining immunity that naturally occurs with advancing age, although not everyone is convinced. Dr. Ershler, for example, believes any decline in immune function is not significant enough in most older people—barring an organ transplant, HIV or other immune-compromised condition—to spur cancer's development. And not every malignancy is associated with advancing age. Some malignancies, such as acute leukemia or Hodgkin's disease, are more frequently diagnosed in younger adults, in part because they require fewer cellular changes to develop cancer, Dr. Ershler says.

Once they take root, Dr. Ershler believes cancers are less aggressive in older patients than in their younger counterparts. He says some of the most common cancers are slower growing and slower spreading, which he attributes to the less fertile environment in aging tissue, with fewer growth and other factors that could stimulate cancer growth.

Other researchers, though, express caution. "With the exception of breast and lung cancer, I think other cancers are worse in older people or not any better," says Lodovico Balducci, MD, another leading researcher in cancer and aging. And some breast and lung malignancies may have developed earlier in life, but because of their slow-growing nature, might not have been identified until later years, he says.

Assessing Patients

Sometimes the aches and other discomforts of advancing years can mask cancer symptoms and, thus, the diagnosis, says Dr. Balducci, head of the Senior Adult Oncology Program at H. Lee Moffitt Cancer Center in Tampa. Constipation may be written off as normal, or new bone pain may be attributed to arthritic joints. That's why regular screening is crucial, he says.

Once a patient is diagnosed, an oncologist must consider several factors as treatment options are discussed. Will the cancer shorten the patient's life expectancy or, will they most likely die of something else? Even if their life might not be cut short, will the tumor make their remaining years more miserable? And, is the patient healthy enough to withstand the treatment itself, as well as any long-term consequences?

Given the relatively long survival for early-stage prostate cancer, for example, it can make sense to closely watch the malignancy in older patients, only treating when necessary, Dr. Balducci says.

Age may also play a critical role in the decision of whether to give chemotherapy following surgery, known as adjuvant treatment. Adjuvant chemotherapy in a 70-year-old woman allows for a small reduction in the risk of dying of breast cancer, but also carries a small but worrisome risk of complications, including developing heart damage or even acute leukemia, he says. Meanwhile, not all 70-year-olds have the same health status, even before cancer looms.

Oncologists could benefit from a quicker analysis, one that could be done in the doctor's office to gain a snapshot of the patient's ability to withstand the rigors of treatment. Dr. Extermann is working on such a shorthand test.

Geriatricians will often refer to a patient's functional age—an estimation of a patient's relative fitness and frailty—along with their calendar age, and use a comprehensive series of tests to determine their functional abilities. These functional tests look at everything from mobility and comorbidities to cognition and social support.

Oncologists could benefit from a quicker analysis, one that could be done in the doctor's office to gain a snapshot of the patient's ability to withstand the rigors of chemotherapy and other treatment, says Martine Extermann, MD, PhD, an associate professor of oncology and medicine at Moffitt Cancer Center. Dr. Extermann is working on such a shorthand test, one she hopes will require just five minutes, similar to how the Apgar scoring is used to quickly assess a newborn's condition immediately after delivery.

The functioning test would help sort out those patients in vigorous health from those who require additional scrutiny, Dr. Extermann says. About half of older patients likely would require a more detailed functional assessment, she says.

After recovering from two operations, first a lumpectomy and then a mastectomy, Jean Caldwell recalls Dr. Stewart asking, "Are you ready to go on?" Yes, she responded.

Dr. Stewart, medical director of the University of Wisconsin Breast Center, has treated some older patients with portions of the multi-stage treatment Caldwell is undergoing. Caldwell, he says, remains one of the oldest to receive all of the medications. Her cancer is potentially curable, he points out. She's in excellent health and could potentially live another 10 to 15 years.

And despite the stereotype that aggressive chemotherapy should be limited in older patients, Caldwell has had few side effects so far. In December 2006, she completed four rounds of chemotherapy with Adriamycin® (doxorubicin) and Cytoxan® (cyclophosphamide), and is now receiving Herceptin® (trastuzumab) and Taxol® (paclitaxel) with an aromatase inhibitor.

She's suffered some queasiness, but no vomiting. Despite becoming easily winded, she was able to attend the Christmas gathering of her water aerobics group. "She's kind of behaving like a 50-year-old," says Dr. Stewart, describing Caldwell's response to treatment.

Treatment Complexities

Research into older patients' ability to withstand chemotherapy remains limited. But one study published in 2003, involving 37 patients age 70 and older, found the toxicity could be tolerated without a substantial decline.

“Despite having side effects, [the patients] remained fairly functional during chemotherapy,” says Dr. Extermann, one of the study’s researchers. “They were having some difficulty doing their daily tasks, but they were able to do them, in general, independently.”

The development of anti-nausea medications, such as Aloxi® (palonosetron) and Emend® (aprepitant), as well as growth factors like Aranesp® (darbepoetin alfa) and Neulasta® (pegfilgrastim) to boost depleted blood cell counts, has enabled doctors to offer chemotherapy to older and older patients, says Dr. Cohen. Traditionally one of the biggest concerns about chemotherapy has been the drugs’ impact on bone marrow, he says. The ability of older patients to produce red and white blood cells appears to be more limited when their bodies are subject to the toxic stresses of chemotherapy. Newer targeted therapies don’t appear to place such strain on the bone marrow, he says. Still, there’s often a trade-off because the newer agents may have potential effects on the heart or other organs.

Dr. Cohen and other physicians interviewed for this article most frequently mentioned two types of chemotherapy they would use with more caution, depending upon an older patient’s other health conditions. Taxane-based chemotherapy, such as Taxol, can be associated with numbness and tingling in the fingers and toes, a condition known as neuropathy that can become severe. Anthracyclines, which include Adriamycin, can weaken the heart muscle and might not be a good approach in a patient with a history of heart disease (see “Hazardous to Your Heart,” page 22). Other drugs can be substituted, such as methotrexate and 5-FU or Doxil® for Adriamycin. Other cancer drugs can also cause neuropathy, including Velcade® (bortezomib) and cisplatin, and heart damage, such as Herceptin.

Surgery, not surprisingly, also carries its own challenges. Garrett Walsh, MD, a surgeon at M.D. Anderson Cancer Center in Houston, is performing surgery on people with lung cancer and other thoracic malignancies in their 70s and early 80s, and sometimes even older. “Age, by itself, becomes less of an issue if the patient is otherwise healthy,” he says.

But he’s quick to add that you can’t underestimate the potential impact of a major operation. Close monitoring during recovery is crucial, he says. Older patients can become more easily dehydrated. They don’t necessarily spike a temperature if they develop pneumonia. Moreover, if left unaddressed, depression or inadequate pain control can discourage patients from moving around and performing the breathing exercises vital to keeping their lungs clear. “Once you get a [medical] complication in an older patient, their reserve is much less and a snowball effect can occur,” Dr. Walsh says.

How Aggressive?

The practical reality for oncologists is that the patient sitting in their office might not look anything like the older patient who qualified for a clinical trial. Oncologists prefer to make treatment decisions based on research studies. Where older patients are concerned, though, the evidence can be slim at times.

“What we need now and are going to desperately need as the next couple of decades go by,” Dr. Stewart says, “are studies that provide solid evidence of treatment benefit and toxicity in people in the older age ranges. As time goes by, there are just going to be a lot of people who are over the age of 85 and are very functional. When they get cancer, what are we going to do?”

Dr. Ershler points to the work of the Geriatric Oncology Consortium, a group of researchers that’s trying to better understand the diverse needs of older patients. (Drs. Ershler and Balducci sit on the consortium’s scientific advisory board.) One of the consortium’s primary goals is to include a variety of older cancer patients in research studies, including those with other medical conditions besides cancer, says Robert Hauser, PharmD, PhD, chief operating officer for the nonprofit group.

“What we need now and are going to desperately need as the next couple of decades go by are studies that provide solid evidence of treatment benefit and toxicity in people in the older age ranges.” —James Stewart, MD

Jean Caldwell is certainly not alone in fighting back aggressively against cancer. In a 2003 study designed to assess attitudes toward chemotherapy among 195 French and American cancer patients, both groups were surprisingly open to undergoing strong chemotherapy: 70.5 percent of the American patients and 77.8 percent of the French. Their average age: 77 years old.