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## **Health Business Thrives on Unproven Treatment, Leaving Science Behind**

By GINA KOLATA and KURT EICHENWALD

For years, Larry Norton tried to conduct a medical study to determine, once and for all, whether bone marrow transplants could really save the lives of women desperately ill with breast cancer.

His efforts -- and those of dozens of other doctors -- were largely futile. Year after year, few women were willing to participate in the clinical tests, which, to be scientifically valid, required patients to be randomly assigned to either the experimental treatment or standard chemotherapy.

Many believed the experimental treatment was their only hope, and were unwilling to leave anything to chance. So most chose to get transplants from a growing number of hospitals and cancer centers that are part of a multimillion-dollar industry that sells experimental treatments. There, for more than a decade, many women were told that the procedure was the only thing that could save their lives -- when, in fact, no one knew for sure whether it was better or worse than the standard treatment.

"I got so angry," Norton said. "Fifty years from now, we will look at this period with horror and say 'How could this have happened.' "

But Norton, head of the division of solid tumor oncology at Memorial Sloan-Kettering Cancer Center in New York, said he understood why the women refused to join the study: Few patients, faced with advanced and likely fatal disease, would risk passing up a supposedly cutting-edge treatment simply to advance scientific knowledge.

Experts say that tens of thousands of such personal decisions, made under enormous emotional strain, are significantly slowing the search for cures for dire diseases like cancer. The wide availability of unproven procedures sops up the vast majority of potential test subjects, they say, making it difficult, or impossible, to assess which treatments work and which do not.

An increasing number of untested treatments are being sold to desperate patients with ailments like cancer, heart failure and Parkinson's disease. Today, experimental procedures can be purchased outright from community hospitals, university medical centers and even from publicly traded companies.

To better understand the workings of this system, The New York Times examined one of the most widely offered procedures -- bone marrow transplants for solid tumor cancers like breast cancer. The examination found that this procedure entered the medical marketplace in the 1980's before studies to test its effectiveness had even begun. By the time testing was under way, the business had taken on a life of its own. Patients were unavailable and tests were delayed for years or had to be abandoned.

The issue arises because medical procedures, like the bone marrow transplants or new surgical techniques, are not regulated, reflecting the Government's usual reluctance to interfere with doctors' practice of medicine. By contrast, Federal rules require that new drugs or devices like a heart valve be proven safe and effective before being sold to the public.

Doctors, of course, can voluntarily regulate themselves and those in one tiny specialty, pediatric cancer, have done so. These doctors have agreed to provide experimental procedures only to patients who participate in valid research. In that specialty, the availability of a pool of test subjects assures that new ideas for treatments are rapidly tested, allowing them to be adopted nationwide if they work, or tossed aside if they prove useless. As a result, the advances in this field have been phenomenal, far outracing anything seen in adult medicine.

"Too often people have access to therapies that are not proven," said Fran Visco, president of the National Breast Cancer Coalition, a patient group. "As a result, we don't get enough individuals to participate in the clinical trials, so it takes a long time to get answers, or we never get answers."

In breast cancer, testing of bone marrow transplants took twice as long as anyone expected. Throughout the 1990's, doctors and hospitals reported to a national registry that about 15,000 women had purchased bone marrow transplants for treatment of breast cancer. Medical experts said that the voluntary reporting system missed about half of the women who actually received the procedure. Yet, while as many as 30,000 women had bone marrow transplants for breast cancer, only 1,000 participated in the scientific studies.

In ovarian cancer, it proved impossible to even conduct a trial of bone marrow transplants. Doctors at more than 100 medical institutions nationwide spent two and a half years seeking 285 women who would participate. They enlisted just 25. Last April, researchers admitted defeat. The ovarian cancer trials collapsed.

Many doctors, like Maurie Markman, director of the Taussig Cancer Center at the Cleveland Clinic, were unable to enroll a single patient despite monumental efforts.

"It's a tragedy that we can't do a randomized trial in the United States to answer this," Markman said. "Unfortunately, if someone says they can cure you and I say I can't, it is very logical that people will drift to those who can give you hope."

Those who sell experimental procedures have a different view. They say they are helping patients who have run out of options and that researchers who are only focused on determining whether a treatment works are out of touch with the needs of patients suffering with a disease now.

"These are not guinea pigs, this is not a fascist society," said William H. West, chairman of Response Oncology, a publicly traded, for-profit company that sells the procedure. "We are an open marketplace, and that's true in clinical trials."

But other experts point out that the same arguments could be made about drugs and medical devices. In those cases, the Government has decided that treatments must be proven safe and effective before they are offered on a large scale. Abandoning that standard for procedures, these experts said, is perilous.

"Physicians must demand the same high standards of science for new procedures as we do for new medicines," said C. Warren Olanow, professor and chairman of the department of neurology at the Mount Sinai School of Medicine in New York. "The alternative is uncontrolled human experimentation."

Today, in bone marrow transplants, the uncertainty lives on, tearing at women as they face the decision of whether to undergo this difficult procedure. With so many years having passed since the idea of bone marrow transplants first emerged, they struggle to understand how a medical system so advanced could not yet answer a question so basic: does the treatment work?

Catherine Porter, 44, who has breast cancer that has spread to other parts of her body, is among those wondering. Seven years ago, Mrs. Porter, of Imlay City, Mich., had a breast removed to combat her cancer. She felt certain she had been cured. Then, recently she learned the cancer was back, worse than ever. Figuring she would take a gamble, she elected to have a bone marrow transplant two weeks ago at the Barbara Ann Karmanos Cancer Institute in Detroit.

Last week, she arrived home. Now, she waits, wondering if the experimental treatment she received will help her, and why medical science still cannot answer that question for so many thousands of women.

"Something has got to be done," she said, "So we don't have to keep doing this."

## The Procedure: Early Success Leads to Competition

Gabriel Hortobagyi was something of a rebel.

In 1979, when the options for treating breast cancer were limited, Hortobagyi was one of a handful who ventured into uncharted territory: treating the cancer with a bone marrow transplant. When the first patient appeared to do well, Hortobagyi offered the procedure to another woman, and another.

It was not an easy procedure. Known within the field as high-dose chemotherapy followed by bone marrow transplant or stem cell rescue, the experimental treatment is based on a simple concept: if a little chemotherapy killed some of the cancerous cells in a woman's body, a lot might kill them all.

So doctors remove some bone marrow or red blood cells from the patient, then load her with huge amounts of toxic drugs, quantities that destroy the bone marrow. The hope is that the high doses will eliminate the cancer and that the saved bone marrow, when returned to the body, will grow back quickly enough so that the patient does not die from infection. A version of the procedure, using donations of bone marrow, had long been established as effective for blood cancer, but solely because the cancer was in the marrow that was being replaced. The use of the treatment for breast cancer involved a completely different -- and untested -- reasoning.

Even though Hortobagyi and a handful of other pioneers at academic centers selected patients who were young and otherwise healthy, they could not save some from the terrible effects of the powerful anticancer drugs. Fifteen to 20 percent of the women in those early days died from the harsh drugs alone; others had permanent injuries, including hearing loss, nerve damage and heart damage.

The outlaws became heroes by the late 1980's, when they began announcing what looked like amazing outcomes. The data were not scientifically valid proof that the treatment worked -- each medical center looked at less than a few dozen patients and had to infer how they would have fared without a transplant.

But the data appeared to make a startling point. Women with advanced breast cancer who had had transplants experienced remission rates of 50 to 60 percent. The general population of women with advanced breast cancer who had received conventional chemotherapy had remission rates of just 10 to 15 percent.

"Those of us who were involved got very very excited," Hortobagyi said. "We told our patients, 'Look at the results we're getting.' "

The patients were not the only ones who looked. With the apparent success of the bone marrow transplants, a new business had been born.

"It seemed so logical," Norton said. "It started getting accepted without clinical trials."

Data from a voluntary registry, the Autologous Blood and Bone Marrow Transplant Registry of North America, show the growth in the popularity of this procedure. The registry, which records about half of the bone marrow transplants in the United States, found that 271 women with breast cancer had transplants in 1989. Two years later the number had jumped to 749. By 1997 there were 2,853 bone marrow transplants for breast cancer reported.

For-profit corporations offering bone marrow transplants emerged by the late 1980's. Response Oncology, one of the first, started offering the procedure in 1989 as part of what it called a "clinical trials program."

That program involved only trials that gave everybody the procedure and watched how they fared. These studies cannot be used to demonstrate whether the procedure is any better than the standard treatment, because there is no comparison group of similar patients. Therefore, there is no way of knowing how the patients would have fared with conventional treatment.

But the trials did help Response Oncology earn profits.

West, the chairman of the company, said the profit margin from bone marrow transplants is 15 percent. All told, Response Oncology brought in \$128 million in revenue in 1998, largely from its cancer centers providing bone marrow transplants.

In large part, the company, based in Memphis, approached the sale of the experimental procedure like any other business. It undercut potential competitors on price, charging \$80,000 per transplant at a time when others were charging \$200,000.

"We've been a very competitive force," West said. "What happened was a battle over the franchise -- who owns high-dose chemotherapy?"

Private hospitals also joined the fray. Institutions like a hospital in Zion, Ill., owned by Cancer Treatment Centers of America advertise heavily for patients and even pay for patients to travel there for the procedure. Hospitals associated with giant for-profit chains, including the Columbia/HCA Healthcare Corporation and Tenet Healthcare, opened bone marrow transplant programs that offered the treatment to women with breast cancer.

But the academic medical centers -- even those trying to recruit patients for clinical trials -- did not stand aside and let all the profits go elsewhere. By the early 1990's virtually every major medical center was offering bone marrow transplants for breast cancer patients and a growing number of community hospitals were offering them as well.

At academic centers, bone marrow transplant programs quickly became "the cash cow for the cancer service," said William McGuire, an ovarian cancer specialist at Mercy Medical Center in Baltimore.

The doctors who provided transplants were rewarded with money and prestige.

"Bone marrow transplanters are kings," said I. Craig Henderson, a breast cancer expert at the University of California at San Francisco. "They usually get a higher salary, they usually get more money. And more important, they have security and power."

Every entity offering the experimental procedure tried a different sales pitch. Some promoted the prestige of their institutions, others the convenience of their locations, others their caring attitudes and patient support, and others, like Response Oncology, their lower prices.

Soon, with competition red hot, a new business spinoff emerged: Doctors, hospitals and companies began selling bone marrow transplants to patients with other types of tumors, like ovarian and brain cancers. But if the breast cancer treatments were based on a theory, these new uses were theories on a theory.

"It is a technology based on a hypothesis," McGuire said.

Paying for the procedures turned out not to be a problem for many patients: Their insurance companies ended up footing the bill. The insurers at first refused, pointing out clauses in their policies saying they would not pay for experimental procedures. But under pressure from patients, doctors, lawyers and lawmakers, most insurance companies gave in.

Take the case of Rita Hartmann, a 60-year-old elementary school teacher from Wooster, Ohio. When her ovarian cancer recurred, Mrs. Hartmann and her husband agonized over what to do. Cancer Treatment Centers of America told her she had a 30 percent chance of a cure if she had a transplant, but her insurance company said it would not pay. Mrs. Hartmann's husband wanted to mortgage their house, sell all they owned to raise the money. But Mrs. Hartmann held back. "I said, 'That's too traumatic,' " she said.

Instead, she called a staff aide for her Senator, Mike DeWine, a Republican. The aide in turn reached Mrs. Hartmann's insurance company. In addition, Mrs. Hartmann and 20 of her friends wrote pleading letters to her insurer. Three months later, on Valentine's Day last year, the company agreed to pay. Mrs. Hartmann had her transplant.

Her cancer returned within nine months.

Under pressure from doctors and patient groups, Congress even mandated in 1994 that insurers for Federal employees pay for bone marrow transplants for women with breast or ovarian cancer. Soon, lobbied by doctors,

hospitals and patient groups, about a dozen states adopted their own mandates that the experimental procedure be covered.

Lost in the rush to offer the treatment to more cancer patients with solid tumors was the fact that the procedure still had not been shown to work even for breast cancer, where it got its start.

"It evolved into a standard of care," said John Glick, director of the Cancer Center at the University of Pennsylvania. "It isn't."

### The Patients: Rejecting Trials in Quest for a Cure

The poison seeped through the catheter implanted in Deborah Holmes's chest, slowly destroying cells throughout her body. The bone marrow transplant was painful and experimental, but Ms. Holmes believed it her only real hope of beating her ovarian cancer. With it, the doctors performing the procedure assured her, she had a 30 percent chance of wiping out the malignancy; without it, they said, she would probably die.

After being assured that her insurance company would pick up the \$150,000 bill, Ms. Holmes traveled halfway across the country for the treatment, from her home in Hamden, Conn., to the hospital in Zion, Ill., operated by Cancer Treatment Centers of America. To Ms. Holmes, it was worth the trip. "There was so much hope there, so much positive energy down to the nurses and the doctors," Ms. Holmes said.

At Brown University in Rhode Island, a 90-minute drive from Ms. Holmes's home, the mood was far less positive. Despite the happy assurances of 30 percent cure rates at places like Cancer Treatment Centers, researchers at the university knew the truth: No one could say whether this procedure worked for ovarian cancer patients like Ms. Holmes.

Brown was part of a consortium of institutions scouring the nation for just 285 women with ovarian cancer to participate in research to determine whether bone marrow transplants prolonged lives. But with so many desperate patients like Ms. Holmes flying anywhere to get the experimental treatment, finding test subjects was almost impossible. On April 25, after two years of trying to enroll women, researchers admitted defeat.

Ms. Holmes, unaware of the national clinical trial, believed what Cancer Treatment Centers of America had told her -- that transplants could cure women like herself. When her cancer returned last November, five months after her transplant, Ms. Holmes said she guessed she was just one of the unlucky ones.

She died on Aug. 14.

The collapse of the ovarian cancer trials underscores the problems with the current system for selling unproven medical procedures. Even though there may be plenty of patients eligible to join such studies, they may be unwilling to participate when they can obtain the procedure elsewhere.

Breast cancer clinical trials had begun several years before, in 1990, but struggled to find patients. There were two national trials: one for women whose breast cancer had spread throughout their bodies and another for women whose cancer had spread to at least 10 of the lymph nodes under their arms. Researchers expected it would take about three years to enroll about 1,000 women in the two studies. Instead it took seven years. For every 10 women who could have been in a clinical trial, 1 actually enrolled, Norton said.

That is not so surprising, Henderson said. Patients in the clinical trials must sign a consent form spelling out their grim prognosis and stating that there is no evidence that bone marrow transplants are any better than the standard therapies.

To enter the trial, he said, "you have to face these realities, which is never easy."

But if the patient has a transplant outside a trial with a control group of patients, known as a randomized trial, enthusiastic doctors may tell her that a transplant could save her life. Although patients "have a right to the truth," Henderson said, they understandably "are not going to go to doctors who take away hope"

Medical centers had to make a choice: Offer only the randomized clinical trials -- and watch patients leave in droves -- or offer bone marrow transplants outside the randomized trials for those who would not participate in the research studies.

Andrew L. Pecora, chief of the adult blood and marrow stem cell transplant program at Hackensack University Medical Center in New Jersey, gave women an option of having a transplant outside a randomized trial. "I offered the clinical trial to every patient," he said. "But I did not force them to do it." Few entered the trial, he said.

Norton refused to provide transplants outside the trial. His patients went elsewhere. "I was disheartened but I wasn't surprised," he said.

As the business was booming and the trials staggering, Hortobagyi, one of the pioneers who had helped get transplants started, was having second thoughts. Those initial stunning results he and others had reported were with carefully selected patients younger than 60 and otherwise healthy -- no heart disease, no emphysema, nothing that might make the high doses of drugs even more risky.

The researchers had compared their outcomes with the outcomes with conventional chemotherapy for all women with advanced breast cancer, even though most breast cancer patients were older and sicker than those who had transplants. Hortobagyi decided to go back and compare the outcomes in the women who had transplants with those of women who were just as young and healthy but who had conventional chemotherapy.

The women, he discovered, did just as well when they had conventional chemotherapy. The women he had provided with transplants did not survive in greater numbers because of the procedure. They survived because they were healthier to begin with.

It was a hard fact to face.

In promoting transplants, "we deceived ourselves and we deceived our patients," Hortobagyi said. "We oversold it."

But that realization came too late.

### The Future: Dismay as Results Prove Disappointing

Last May 17 a crowd of breast cancer specialists filled a conference room half the size of a football field at the Georgia World Congress Center in Atlanta. Those who came too late to get seats spilled into two smaller rooms nearby with closed circuit television screens. Few at the annual meeting of the American Society of Clinical Oncology wanted to miss this moment when the leaders in their field would present the long-awaited data from clinical trials of bone marrow transplants for women with advanced breast cancer.

Five studies had been completed -- two large clinical trials from the United States, two large trials from Europe, and a small one involving 154 women from South Africa. In all, about 2,000 women had been randomly assigned to have the experimental procedure or conventional chemotherapy and enough time had elapsed to ask if the women who had transplants lived longer than those who did not have them.

The results were not the triumph that many had hoped for.

In four of the five clinical trials, there was no difference in survival between women who had transplants and those who had conventional therapy.

Only in the South African study did the women who received bone marrow transplants outlive the patients in the group who received standard therapy. But on closer inspection of the data, even that success seemed suspect: the women who had transplants lived about as long as the women in the other studies. But the women who had conventional chemotherapy in the South African study did far worse. The results did not indicate that transplants improved survival, but that the outcomes for the control group were poor.

No one on the podium that day claimed that the studies showed that transplants were a triumph. Indeed, the trials' failure to show the expected benefits of transplants gave rise to a troubling question: When the best available data provided no evidence that bone marrow transplants were any better than conventional chemotherapy, should transplants continue to be promoted and sold?

For the National Breast Cancer Coalition, which represents cancer patients, the data spoke for themselves: Bone marrow transplants had been tested and had failed.

"How can anybody look at these data and think this is something we should continue doing or that they are inconclusive?" asked Ms. Visco, the coalition's president. The group put out a news release saying, "It is time to move beyond the infrastructure" created around transplants.

But cancer specialists were less definitive. Many said they still saw promise in transplants, arguing that it was too soon to say for sure that the procedure offered no benefits. They urged that nothing change for the time being while the women in the studies were followed for longer periods to see if those who had transplants eventually did better. They also said that chemotherapy had improved over the last decade and because the studies used older drugs, it remained possible that bone marrow transplants with new drugs might be better than conventional chemotherapy.

Reflecting these views, the American Society of Clinical Oncologists put out a news release saying that the papers presented at the meeting "report mixed early results" and that more years of study are needed.

Allen S. Lichter, the departing president of the society and dean of the University of Michigan Medical School, urged that nothing change for the time being while new studies get under way and the women in the initial studies continue to be followed.

"As a nontransplanter and a keen observer of this research, I don't think there is enough information to say it should die," Lichter said.

He also said that because not every woman is eligible for a clinical trial or has ready access to one, transplants should still be available outside trials. "I for one am not ready to say that this should only be done in a clinical trial," Lichter said.

West of Response Oncology said his company intended to keep selling transplants. Calls to stop offering them are "an oversimplification," he said, because the trials were not definitive. More trials and years of further study are needed, he said.

At bottom, he said, critics are missing the point. What matters, he said, is not whether the treatment has been shown to work but whether studies are producing more knowledge.

"You could say there was only one important question and you didn't answer that one," West said. "I know you want to think of it as a drug that either works or doesn't. I think of it more as a platform that needs to be modified and studied."

So now oncologists and companies say they will press ahead, continuing to sell a painful, expensive procedure that the best available science says is no improvement over standard care, which is less traumatic. Some patient advocates and doctors find this a troubling abandonment of the rigors of science.

"I don't have a problem with oncologists who say, 'We really have to do something for these patients, they are facing a terribly short future,' " said Alan Garber, a professor of medicine at Stanford University. "The problem is when they start to do things that have been tested and have not proven effective. Then you are leaving the arena of science and going into blind faith."

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