In Costly Cancer Drug, Hope and a Dilemma

By GINA KOLATA and ANDREW POLLACK

It took only an instant for 58-year-old Gailanne Reeh to go from the picture of health to death's door. By chance, her doctor noticed a lump under her arm during a routine exam. It turned out to be advanced breast cancer.

Soon she was having tests to reveal the extent of the cancer and hearing the grim results.

The surgeon, she recalled, "looked at me and said: 'This is not a conversation I like to have. But I can't do anything for you. You can't be cured. You can't be treated. All we can do is manage your cancer.' " On scans to detect tumors, the doctor told Ms. Reeh, "you light up like a Christmas tree."

And so, like many others in that situation, Ms. Reeh, the vivacious owner of a staffing agency in Boston, was given bevacizumab, also known as Avastin, a drug that signifies both the hopes and dilemmas of modern medicine.

Looked at one way, Avastin, made by Genentech, is a wonder drug. Approved for patients with advanced lung, colon or breast cancer, it cuts off tumors' blood supply, an idea that has tantalized science for decades. And despite its price, which can reach $100,000 a year, Avastin has become one of the most popular cancer drugs in the world, with sales last year of about $3.5 billion, $2.3 billion of that in the United States.

But there is another side to Avastin. Studies show the drug prolongs life by only a few months, if that. And some newer studies suggest the drug might be less effective against cancer than the Food and Drug Administration had understood when the agency approved its uses.

While many patients and their doctors say the drug can improve the quality of life -- like a sense of well-being and an ability to carry out daily tasks without exhaustion or pain -- such effects can be hard to document. Meanwhile, many patients with cancers other than those of the colon, lung or breast are taking the drug, even in cases where there is no compelling evidence that it can help.

Avastin also has serious, if infrequent, side effects, some of which can be lethal. And because it is almost always used with standard chemotherapy -- it did not work as well when researchers tried it alone -- patients on Avastin do not escape chemotherapy's side effects.

"I still use Avastin routinely, but it's sobering," Dr. Leonard Saltz, a colon cancer specialist at Memorial Sloan-Kettering Cancer Center in New York, said of the new data. "It's not a slam dunk and, in fact, the incremental benefit may be more modest than we want to admit."
If Avastin were inexpensive or if it cured cancer or even held it at bay, as the drug Gleevec does for blood cancer, few might care. But like a half-dozen or so new biotechnology drugs with a similar combination -- alluring promise, high price and only arguable benefits -- Avastin raises troubling questions:

What does it mean to say an expensive drug works? Is slowing the growth of tumors enough if life is not significantly prolonged or improved? How much evidence must there be before billions of dollars are spent on a drug? Who decides? When, if ever, should cost come into the equation?

For a patient like Ms. Reeh, fighting for her life, the cost is not the main concern. If her insurer did not pay, she said, she would go into debt, find a way to raise the money.

But some in the pharmaceutical industry worry that such prices will raise concerns about whether the drugs are worth it, leading to a backlash like price controls or restrictions on use.

Roy Vagelos, a former chief executive of Merck who is considered an elder statesman of the industry, said in a recent speech that he was troubled by a drug, which he would not name but which was a clear reference to Avastin, that costs $50,000 a year and adds four months of life. "There is a shocking disparity between value and price," he said, "and it's not sustainable."

Some patient advocates are also troubled by very expensive treatments like Avastin coming into routine use on what they see as little more than a hope and an expensive prayer.

"It's absolutely critical that we start having a public discussion," said Barbara Brenner, executive director of Breast Cancer Action, an advocacy group. "I think of Avastin as a model that is showing us where the problem is."

The Rising Cost

The problem is largely one of cost.

Cancer drugs constitute the second biggest category of drugs in the United States behind cholesterol-lowering medicines, and accounted for $17.8 billion of total prescription drug sales of $286.5 billion in 2007, according to IMS Health, a health care information company. Spending on drugs for cancer grew 14 percent last year, faster than for all but three other diseases.

About 100,000 Americans take Avastin, according to Genentech's data. The drug is being formally tested in as many as 450 clinical trials for about 30 types of cancer. And Genentech, its partner Roche and the National Cancer Institute are now starting studies that will include more than 26,000 people with lung, colon or breast cancer at earlier stages of the disease than were studied initially. If Avastin is approved for those earlier-stage patient groups, it could have a major impact in delaying the return of their cancer, but hundreds of thousands of additional people could end up taking it, possibly for years.

And that, insurers and patient advocates say, could impose a considerable financial burden.

The drug's price, as charged by Genentech, can be $4,000 to more than $9,000 a month, depending on a patient's weight and the type of cancer. Avastin's cost to patients and insurers can be much higher, though, because doctors and hospitals buy the drug and then sell it to patients or their insurers, often marking up the price. So the $2.3 billion that Genentech recorded in sales of Avastin represents only part of what Americans
spent on the drug last year.

And while doctors typically want the best for their patients, there also are other factors that may push them to prescribe Avastin.

"Think about where the interests are aligned," said Dr. Deborah Schrag, a colon cancer specialist at the Dana-Farber Cancer Institute in Boston. "Patients who seek out cancer care are often quite willing to try all kinds of things. Doctors want to help them and may be financially incentivized. And it is often quite hard for insurance companies to intervene."

Medicare requires that the doctor or hospital buying Avastin be paid an amount equal to Genentech's average selling price plus a markup of 5 to 6 percent. Of that amount, Medicare pays 80 percent and the patient pays 20 percent. Doctors and hospitals typically do not make much money on Avastin for Medicare patients, and can even lose money if they buy the drug at a price that is higher than average. But patients can end up paying thousands of dollars a month. Some have supplemental insurance to take care of it; others do not.

But private insurers sometimes pay several times as much as Medicare pays for Avastin. Doctors and hospitals have at times charged as much as $35,000 a month for the drug, said Dr. Peter Dumich, who reviews claims for cancer patients for AWAC, a company that helps employers contain health care costs. The insurers have little choice, Dr. Dumich says, when their contracts say they must pay a portion, like 80 percent of the charge, whatever the charge actually is. "Providers have them over a barrel," he said.

And, like Medicare, private insurers may in turn require patients to pay a percentage of what can be hefty bills. That has happened to Jim Lemieux, a colon cancer patient at Dana-Farber. His private insurance requires that he pay 25 percent of the cost of his treatment, which includes Avastin. His insurer, he said, is charged $6,000 a month for the drug, making his share $1,500.

Mr. Lemieux, who was a sales manager at a car dealership, says he cannot bear to look at his medical bills. They include bills for hospitalizations and surgery and co-payments for standard chemotherapy, as well as Avastin.

To try to make ends meet, he and his wife just sold their house and are moving into their son's basement. Even so, he says, he expects he will have to file for bankruptcy.

"You figure you've got insurance," Mr. Lemieux said. "I paid 30 years and never got sick. I should have just paid the money to myself."

But he is not planning to give up Avastin.

"I'm trying to stay alive," Mr. Lemieux said. "I decided I'm not going to die from Stage 4 colon cancer."

A Promising Dream

When Napoleone Ferrara was hired by Genentech in 1988, he was assigned to work on a drug to ease labor during childbirth. But he could not get cow pituitary glands out of his mind.

Dr. Ferrara had noticed in his previous academic job that when he mixed extracts from the glands with cells
from blood vessels, the vessel cells started to grow rapidly. Something made by those glands, he reasoned, could spur vessel growth. He found that substance in 1989 and called it vascular endothelial growth factor, or VEGF (pronounced VEJ-eff). He even isolated its gene. And that led to a new idea for a cancer drug.

It drew from a hypothesis for a sort of universal cancer treatment, advanced by the late Dr. Judah Folkman of Harvard. Dr. Folkman had argued, starting in 1971, that tumors must grow their own blood vessels to bring them nourishment and oxygen. If you could choke off those vessels, Dr. Folkman said, you could halt cancers.

Dr. Ferrara and his colleagues realized that if they could block VEGF, cancer cells might not be able to grow blood vessels. So Genentech developed a monoclonal antibody, a type of protein, that would bind to VEGF and disable it. In 1997, the company began testing its antibody, which became Avastin, in cancer patients.

There were some setbacks. Avastin failed in its first big clinical trial, against very advanced breast cancer. Genentech's stock dropped 10 percent in one day, and some analysts questioned whether the company's investment would ever pay off.

Meanwhile, the company was well into a trial of Avastin for colorectal cancer. Patients got chemotherapy plus either Avastin or a placebo. The Avastin patients lived more than four months longer, a median of 20.3 months, compared with 15.6 months for the other group. "We were excited," Dr. Schrag said. "Four months is big."

In February 2004, 15 years after Dr. Ferrara's initial discovery, the Food and Drug Administration approved Avastin for patients with advanced colon cancer. A blockbuster was born.

But now there is a question mark over that evidence. That first exciting result compared Avastin with a type of chemotherapy that has since been widely replaced by a more effective regimen.

In a later, larger study comparing Avastin with current chemotherapy, Avastin slowed the growth of tumors but did not extend life by an amount considered statistically significant.

Dr. Schrag said she would continue to give the drug to her colon cancer patients. But when she talks to patients about Avastin now, she said, she will add a few more caveats.

She believes that some patients are helped -- that they may feel better and, she hopes, may even, in some cases, live longer. She says a few of her Avastin patients lived several years and some are still alive. Of course, she acknowledges, there is no proof that Avastin was responsible, but it is stories like those that give her, and patients, hope.

"All patients want to be the tail end of the survival curve," Dr. Schrag said.

When Avastin was approved for colon cancer, Genentech decided to charge $2,200 for an average dose, taken every two weeks. That was a reflection of the research and development it had put into the drug as well as continuing research, said Walter Moore, the company's director of government relations.

Genentech, which has never before revealed what it spent to develop Avastin, now says that it and its partner Roche have spent more than $2.25 billion starting with Dr. Ferrara's original work. The figure includes research, clinical trials and filing for regulatory approval and is well beyond what was spent by the federal government, which conducted important clinical trials of Avastin. Through May 2006, the government had
spent $44.6 million on Avastin trials and related laboratory work, according to figures obtained from the National Cancer Institute by Consumer Watchdog, an advocacy group.

While it is impossible to compare directly the company's investment to the costs of developing other cancer drugs, the amount Genentech says it spent is "on the high side" of the industry average, said Henry Grabowski, a professor of economics at Duke University who has analyzed drug development costs.

Genentech says it and Roche -- which owns a majority of Genentech and markets Avastin outside the United States -- will spend an additional $1 billion testing Avastin as a treatment for early-stage cancers.

The price also reflected Genentech's perceived value of the drug compared with other cancer treatments. The price was half that of Erbitux, a colon cancer drug from ImClone Systems and Bristol-Myers Squibb that was approved the same month as Avastin and had not been shown to prolong life.

But Avastin is typically used for a longer time and by more patients than Erbitux. And the Avastin dose for lung and breast cancer is twice that for colon cancer, doubling the price.

Eric Schmidt, an analyst at Cowen and Company, said pharmaceutical companies typically based drug prices on what the market could bear.

"It's high because Genentech can price it high," he said, noting that Avastin's price was in line with that of some other cancer drugs. Despite the company's research and development costs, Mr. Schmidt said, Genentech is one of the most profitable of pharmaceutical and biotechnology companies.

Other countries have different views about whether Avastin is worth its price. An institute that advises the British government on which drugs to pay for recommended against it, saying that the drug was not cost effective based on its cost per year of life extended.

In the United States, Genentech argues that it puts patients first, with free drugs for those who have no way to pay for them and donations to charities that can help with payments. It also capped the price for a year's supply of Avastin at $55,000 (not counting markups by doctors and hospitals) for patients with incomes of less than $100,000 a year.

But progress against cancer has a price, the company says.

"The quest is to eliminate the disease," Arthur D. Levinson, Genentech's chief executive, said at an annual investor meeting. "And, yes, there is going to be a cost to that."

Of Dubious Benefit

After colon cancer, the next target was lung cancer.

Dr. Bruce Johnson of Dana-Farber knew the difficulties well. He had been at the National Cancer Institute, where he reviewed 25 years' worth of clinical trials, 30 studies that started with high hopes and ended with little progress. He used to give talks quoting a World War I general: "Ground gain minimal. Casualties huge. Conclusion -- press on."

Avastin, in that context, looked like something of a triumph. Patients who took it along with standard
chemotherapy survived for a median of 12.3 months, compared with 10.3 months for those getting only chemotherapy. The results were announced in 2005. "Finally," Dr. Johnson said, "something worked."

But as with colon cancer, a newer study adding Avastin to a different chemotherapy regimen has raised questions about its effectiveness against lung cancer. The study's Avastin patients lived no longer than those who got the chemotherapy plus placebo. Although the drug did slow the median time until progression of tumors, the difference was less than a month.

The third approval for Avastin, for advanced breast cancer, came in February of this year. The clinical trial found it significantly slowed the progression of cancer but did not significantly extend life. The F.D.A. went against its own panel of outside experts, who had voted 5 to 4 against approval.

The agency's action has not sat well. Senator Charles E. Grassley, Republican of Iowa, asked the Government Accountability Office to look into the F.D.A.'s approval of Avastin and some other drugs that "appear to have little to no effect in protecting lives and increasing health."

Dr. Lee Newcomer, an oncologist and executive at the insurer United HealthCare, said patients were not well served, and neither were insurers, nor the public, which ultimately foots the bill. If a drug just stops tumor progression, without the woman's living longer or feeling better, without her noticing anything different, Dr. Newcomer said, "you're treating an X-ray."

Patient advocacy groups were split.

"Even when these drugs 'work,' what kind of impact are you talking about?" said Fran Visco, president of the National Breast Cancer Coalition, which opposed approval. "But we market them and give them to everybody."

Yet other doctors and advocates for patients say that when tumors grow, patients can notice new or worsening symptoms. And they certainly experience greater anxiety.

Dr. Kathy Albain, a breast cancer specialist at Loyola University Medical Center in Maywood, Ill., polled colleagues and patients and found overwhelming support for approving drugs based on delaying tumor progression. It would be ideal to show that a drug also prolongs life, but that may not be realistic, she said. The reason is that when a woman's cancer progresses, doctors change the drugs they use, hoping to slow the cancer. That dilutes any impact of the first drug -- in this case Avastin.

Kay Wissmann, director for government relations at the Breast Cancer Network of Strength, a patient advocacy group, said women should have a choice to use Avastin.

"We've got some good evidence about this particular drug," she said, "so maybe we should let the people with metastatic disease have the option of using it."

Unapproved Uses

Then there are patients who cannot wait for evidence that a drug works for their cancer.

One patient's husband had no medical training. But he determined through his own literature search that his wife's form of brain cancer produced a lot of VEGF, the very substance Avastin neutralized. So the couple wanted to try Avastin, even though it had never been tested for brain cancer. It was 2004, when the only
Avastin approval was for colon cancer.

They asked the woman's doctor, Dr. Virginia Stark-Vance, to give them the drug.

Dr. Stark-Vance, a solo practitioner in Dallas and Fort Worth, was reluctant, worried that Avastin could cause bleeding in the brain. That had happened in one of the earliest clinical trials, when a 29-year-old woman whose liver cancer had spread to her brain collapsed from a hemorrhage while riding her bicycle.

Finally, Dr. Stark-Vance agreed on the condition that the woman be hospitalized to receive Avastin, in case there was a brain hemorrhage. Had there been one, Dr. Stark-Vance "could have lost her license," said Dr. Henry Friedman, a brain cancer specialist at Duke.

Like many others taking Avastin, this woman plunged into the unknown, without the assurance of a clinical trial studying whether the drug worked for her type of cancer.

Doctors are free to prescribe Avastin, or any other drug on the market, for unapproved uses, at their discretion. As much as 75 percent of cancer drug use is of this "off label" variety, according to an estimate by the National Comprehensive Cancer Network, a group of big cancer centers. And some doctors say that with patients dying, they simply cannot wait for airtight evidence.

"Of course we want everything to be evidence-based," said Dr. Yashar Hirshaut, an oncologist in Manhattan. "I also like the American flag and apple pie."

But, he explained, "You say, 'This person is dying right here and I need something that will help, and there's a logical construct that I can see how it will help.'"

One of his patients, Alice Lichter, has had gastric cancer since 2006. Dr. Hirshaut is throwing the whole arsenal at it, giving her gemcitabine, a drug used for pancreatic cancer, plus virtually every drug approved for colon cancer: Avastin, Erbitux, Eloxatin, irinotecan, 5-FU and leucovorin. Most are not approved for gastric cancer.

Once every two to four weeks, Ms. Lichter, 72, flies from her home in Miami and checks into Lenox Hill Hospital in Manhattan, where she undergoes four days of intravenous infusions.

"I call Lenox Hill my second home," she said.

'You Name It, It Got Tried'

Ms. Lichter, whose cancer appears to have receded, said she never questioned Dr. Hirshaut's judgment. And she has no idea how much her drugs cost because Medicare is paying for them and her supplemental insurance covers her co-payment. Insurers say they are often forced by state laws to pay for cancer drugs not approved by the Food and Drug Administration, and Medicare must pay if the drug's use is listed in a compendium, a reference compiled by cancer specialists, whose standards are looser than the F.D.A.'s.

Such requirements are one reason about 12 percent of United HealthCare's Avastin patients have cancers other than colon, breast and lung. "Brain, stomach, pancreas, primary cancers of the liver, bladder, small bowel, larynx, prostate -- you name it, it got tried," Dr. Newcomer said.
But the anecdotes and evidence from small trials that may seem to justify off-label use sometimes turn out to be misleading. That happened with pancreatic cancer. After patients and doctors decided Avastin had to be helping, cancer researchers themselves conducted a large study. So did Roche. Avastin, both studies concluded, did not prolong life for people with cancer of the pancreas.

For brain cancer, doctors are encouraged, although they do not really know for sure whether Avastin helps. The brain tumor in Dr. Stark-Vance's patient shrank so much after two infusions of Avastin that the radiologist who performed the brain scans called Dr. Stark-Vance in wonderment.

Dr. Stark-Vance began treating more patients. Some insurers paid for the drug. Others, including Medicare and Medicaid, did not. But Dr. Stark-Vance said Genentech agreed to provide the drug free for her patients who could not otherwise pay.

As word spread, Dr. Friedman at Duke and Genentech organized studies of a type generally considered less than definitive. There was no control group that took another drug or got a placebo. Everyone got Avastin. Otherwise, no one would enroll in the study, doctors argued.

Then the investigators compared the results with what they thought would have happened without Avastin. The patients lived a median of about nine months, about three months longer than the researchers estimate would have been expected.

But such comparisons have led scientists seriously astray in the past because the people being treated with a new drug often are very different from previous patients who did not take it and because overall medical care steadily improves. Nonetheless, Genentech has said it planned to apply this year to the F.D.A. for approval for Avastin to treat glioblastoma, the deadliest form of brain cancer.

Dr. Stark-Vance said her initial Avastin brain cancer patient broke her hip and had to be taken off the drug because it interfered with wound healing. She eventually died.

But by now, even without an F.D.A. approval, "the whole country" is using Avastin for glioblastoma, Dr. Friedman said.

Better Than Nothing?

Gailanne Reeh remembers what life was like within a few months of those initial scans, when her cancer began causing terrible symptoms.

Her abdomen grew so full of fluid that it was hard to bend to tie her shoes. Bowel movements were difficult, and even lying down was uncomfortable with that huge mass in her abdomen.

She says she was chilled by what she recalls her doctor saying: "There was so much growing so fast in my abdomen and so much in my bowel, it was not a matter of maybe I would get a bowel obstruction. It was when I would get a bowel obstruction," Ms. Reeh said. "And when I got it, there would be nothing anyone could do. I would die."

To try to stave off such a horrible outcome, her oncologist, Dr. Eric Winer of Dana-Farber, offered to enroll her in a clinical trial comparing Avastin with another new biotech drug. Ms. Reeh was assigned to the group that got Avastin in combination with the chemotherapy drug paclitaxel, also known as Taxol.
The study closed after six months, but Ms. Reeh continued with her drug regimen, and her insurer is paying. After six months of treatment the fluid in her abdomen was down to just a trace, her tumors were stable or smaller and she felt like her former self again.

"I'm really, really excited," she said.

Was it the Avastin?

Dr. Winer said he did not know, since Taxol can also shrink tumors. It is impossible to draw conclusions from individual patients, he said. Still, he said, "I think it is quite likely that the combination of Taxol and Avastin improved her odds of having a better quality of life."

Dr. Winer says that when he is not sitting in front of a patient, he thinks about whether drugs like Avastin are worth it to society. But when facing a seriously ill patient, who, based on clinical trial results, might benefit -- even if only a little -- from Avastin along with chemotherapy, he has to think about his patient's needs.

"I can't say, 'Let's not use Avastin; it's a very expensive drug and I am worried about the cost to society,' " Dr. Winer said.

And so, Dr. Winer said, the answer you get when you ask whether drugs like Avastin are worth it very much depends on whom you ask.

"A person who hasn't been affected by cancer will say, 'Gee, why should we pay for an expensive treatment that doesn't extend life when we have other needs?' " Dr. Winer said.

A person like Ms. Reeh will have a different response. She does not want to give up Avastin.

Last month, she reluctantly stopped taking her drugs for a while because Taxol was injuring the nerves in her feet. But later this month she hopes to resume taking both drugs, or at least Avastin.

Ms. Reeh says she knows her cancer may very well kill her eventually. But what is it worth to feel better again?

"It's really about living and not waiting to die," she said.

And what if 5 percent of Avastin patients live a lot longer than they would have without the drug?

"I might be in that 5 percent," she said.

PHOTOS: Gailanne Reeh, who has advanced breast cancer, was treated with Avastin in April. (PHOTOGRAPH BY JOSH HANER/THE NEW YORK TIMES) (pg.A1); EXPERIMENTAL TREATMENT: After participating in a clinical trial comparing Avastin with another new drug, Gailanne Reeh continued the regimen. (PHOTOGRAPH BY JOSH HANER/THE NEW YORK TIMES) (pg.A16); THE BATTLE Above, Gailanne Reeh with her oncologist, Dr. Eric Winer. Left, Jim Lemieux, a colon cancer patient whose treatment includes Avastin. (PHOTOGRAPH BY JOSH HAMER/THE NEW YORK TIMES); THE INNOVATOR: In 1989, Napoleone Ferrara of Genentech made the initial discovery that led to the development of Avastin. (PHOTOGRAPH BY JIM WILSON FOR/THE NEW YORK TIMES) (pg.A17)
In Costly Cancer Drug, Hope and a Dilemma - The New York Times

CHART: SECOND IMPRESSIONS: The Food and Drug Administration has approved the drug Avastin for three types of cancer: colorectal, lung and breast. But in each case, subsequent clinical trials that combined Avastin with different chemotherapy drugs found Avastin to be less effective as a treatment for those cancers than it appeared to be in the original studies on which the F.D.A. based its approvals. (Sources: New England Journal of Medicine; American Society of Clinical Oncology; Food and Drug Administration) (pg.A17)