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HEALTH | NYT NOW

Cancer Researchers Report Longer Survival Rates With Immunotherapy

By ANDREW POLLACK JUNE 2, 2014

CHICAGO — Drugs that unleash the body's immune system to combat tumors could allow patients with advanced melanoma to live far longer than ever before, researchers gathered at the nation's largest cancer conference say.

"It's a completely different world for patients with metastatic melanoma, to talk about the majority of patients being alive for years rather than weeks or months," said Dr. Jedd D. Wolchok, a melanoma specialist at the Memorial Sloan-Kettering Cancer Center, interviewed at the annual meeting of the American Society of Clinical Oncology here.

The treatments, called immunotherapy, generated a huge stir at last year's annual meeting, with some doctors predicting a revolution in cancer care.

Immunotherapy has also set off a frenzy in the pharmaceutical industry, with Bristol-Myers Squibb, Merck and Roche racing to bring drugs to market. Close behind is AstraZeneca, whose work was a major reason behind Pfizer's recent unsuccessful bid to buy that company. Many other drug companies are now scrambling to get a piece of what could become a market worth tens of billions of dollars a year in sales.

At this year's cancer meeting, which is underway here, there are not as many astonishing new results being presented. Some of the findings being highlighted simply involve longer follow-up of patients from the same

studies presented last year.

The new results show the effects of the drugs can last for a long time. And there is now initial evidence that drugs work on a growing number of types of cancer.

But there are grounds for caution. The results are mainly from small studies that lack control groups for comparison. The medicines work for only a minority of patients. And in some cases the drugs are causing frequent or severe side effects. That seems to be especially true when two immune-boosting drugs are used in combination, something that might be necessary to achieve maximum effectiveness.

The power of a combination was shown in advanced melanoma, a deadly skin cancer. In one clinical trial, 79 percent of patients receiving two immunotherapy drugs from Bristol-Myers were alive after two years. Of those who received the optimal dose, the two-year survival rate was 88 percent.

Dr. Wolchok, who was involved in the study, said that only several years ago, the two-year survival rate for metastatic melanoma may have been less than 10 percent. One of the immune drugs, Yervoy, which was approved for use against melanoma in 2011, allows for a two-year survival rate of about 25 percent when used alone, he said. The other drug, nivolumab, which is still experimental, had a two-year survival rate above 40 percent range when used alone.

The drugs block the actions of proteins that act as brakes on the immune system, preventing them from attacking the tumors. Yervoy, also known as ipilimumab, releases the brake known as CTLA-4. But the main interest is in nivolumab and similar drugs coming from Merck, Roche and AstraZeneca that release a brake called PD-1.

Merck could win approval from the Food and Drug Administration to sell its drug as a melanoma treatment by this October. Some 69 percent of patients using the drug, called pembrolizumab or MK-3475, survived one year, according to new results of a 411-patient trial presented Monday. It is too soon to know how many will live two years.

But unleashing the immune system can also lead to dangerous side effects, including colitis, a serious inflammation of the colon, as well as problems with the liver, thyroid and pituitary glands.

When Bristol-Myers tested its two drugs together as a treatment for advanced lung cancer, about half of the 46 patients suffered serious side effects, and three of them died from the drugs themselves, according to an abstract of a study being presented here.

The side effects could be a barrier to using the drugs for less advanced stages of disease.

Results released here Monday show that Yervoy, which is now approved to treat melanoma that has spread beyond the skin, was also effective against melanoma confined to the skin and lymph nodes that could be surgically removed. Three years after surgery, 46.5 percent of patients who received Yervoy remained free of disease, compared with only 34.8 percent of those receiving a placebo.

However about half the 471 patients who started taking Yervoy discontinued treatment because of side effects and five of them died from those side effects.

To be sure, the dose of Yervoy used in that trial was far higher than the dose approved for metastatic melanoma. Pharmaceutical executives and medical specialists say the side effects of the immune drugs are different from those of traditional chemotherapy and doctors have been unprepared. But now they are learning to mitigate them.

“If you see colitis and you’ve never seen it before, you’ll freak out,” said Dr. Padmanee Sharma, scientific director of the immunotherapy program at the M.D. Anderson Cancer Center in Houston. She said that the older chemotherapy drug cisplatin was also once considered so toxic it would never be used. Now, she said, “We give cisplatin like water.”

Besides melanoma, the drugs are known to work against lung and kidney cancers. Bristol-Myers is applying to the F.D.A. for approval to sell nivolumab as a last-ditch treatment for advanced lung cancer.

But at this meeting there were signs that the drugs that block the

action of PD-1 might also work for bladder cancer, head and neck cancer, and ovarian cancer.

In a small study, Roche's drug, known as MPDL3280A, shrank tumors in 43 percent of a subset of patients with advanced bladder cancer. The company might now make bladder cancer the priority for its first approval rather than lung cancer, Daniel O'Day, head of Roche's pharmaceutical business, said in an interview here.

The subset consisted of patients whose tumors produced a protein called PD-L1, which binds to PD-1 on immune system cells and thereby shuts down those cells. Companies are exploring whether a PD-L1 test can be used to determine which patients should get the drugs.

But in Roche's study, 11 percent of the bladder cancer patients whose tumors did not make a lot of PD-L1 also experienced tumor shrinkage. "If you're that patient, it is unethical not to offer it," said Dr. Sharma.

Researchers are also trying to learn why only some types of cancers can be treated with these drugs. One reason could be that other cancers stifle the immune system by means other than PD-1.

"It's hard to believe that a single checkpoint is going to be important in every cancer," said Dr. Mario Sznol, a professor of medicine at Yale, using a technical term for the immune system brakes.

Companies are developing inhibitors of other checkpoints as well as other types of drugs to direct the immune system to attack tumors. Roche by itself is developing 20 immunotherapy drugs, Mr. O'Day said. And the immunotherapy drugs are being tested in combination with one another and with more conventional drugs as well.

Some experts note that there was initially huge excitement about so-called targeted therapies and about drugs that block the flow of blood to tumors. While those approaches have made a difference, they have not been the panaceas enthusiasts envisioned, and that is likely to be the case with immunotherapy as well.

"With anything, all that glitters is not gold," said Dr. Richard Pazdur, who as chief of the cancer division at the F.D.A. has a unique insight into

how drugs are performing. He said he was not allowed to discuss specific drugs.

Correction: June 2, 2014

An earlier version of this article misspelled, in one instance, the surname of the scientific director of the immunotherapy program at the M.D. Anderson Cancer Center in Houston. She is Dr. Padmanee Sharma, not Parma.

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