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DRUG DEVELOPMENT

A chance of survival

People with advanced melanoma are living longer thanks to treatments that target cancerous cells or encourage the immune system to wipe out the tumour.

BY HANNAH HOAG

When Antoni Ribas began treating metastatic melanoma 15 years ago, he faced a lot of difficult conversations with his patients. Few treatments were available for those in the advanced stages of the disease, and none was particularly effective. Patients with stage IV melanoma, which has spread to the lymph nodes or other organs,

had a median survival of just 8–9 months, and only 15% lived for more than 3 years¹.

“I would sit down in front of them and discuss treatments that might work for 10% of them at most,” says Ribas, a medical oncologist at the University of California, Los Angeles. “And I’d say, it probably won’t make a difference if we do treatment or not.”

But things have started to change in melanoma care. Since 2011, the US Food and Drug

Administration (FDA) has approved seven treatments for advanced melanoma (see ‘Treatment of BRAF-mutant melanoma’), including one in September that promotes an immune response against the cancer, and several more are working their way through the process. Drug companies have dozens of treatments in clinical trials.

Targeted therapies, which are tailored to a patient’s genetic make-up and are designed to

disable the cancerous cells, have become the cornerstone for the treatment of advanced melanoma. And drugs that target the immune system and enhance its ability to wipe out cancer cells have just entered the clinic. Patients who had once failed to respond to the meagre range of available drugs are now showing strong, long-lasting responses. “It is an amazing thing,” says Ribas.

HITTING THE TARGET

For many years, cancer was treated according to the organ in which it developed, or by bombarding it with chemicals that killed off rapidly dividing cells. But then researchers began discovering the genetic mutations that transform a normal cell into a cancerous one. These findings uncovered mutant proteins that could be blocked by new drugs, allowing oncologists to selectively target the tumour.

In the late 1990s, oncologists were excited about a new drug called imatinib (Gleevec) that homed in on the cancer cells of patients with chronic myelogenous leukaemia (CML). Most of these patients have an abnormal gene rearrangement that produces a protein that drives the cancer. In theory, drugs that target this protein should cause the cancer to retreat.

This approach was not limited to leukaemia. Another targeted therapy, Herceptin, was shrinking tumours in an aggressive form of breast cancer characterized by mutations in the *HER2* gene². Such successes left cancer researchers looking for similar mutations that push cells to develop into melanoma.

In 2002, researchers working on the Cancer Genome Project at the Wellcome Trust Sanger Institute near Cambridge, UK, uncovered one of melanoma’s weak points. They found that two-thirds of melanomas have a tiny change in the gene encoding a protein called BRAF that is part of a signalling pathway in the cell. The mutation changes one amino acid in the protein³, altering the pathway so that the cells multiply without limit⁴. “When I first saw that paper, it stopped me in my tracks,” says Keith Flaherty, an oncologist at Massachusetts General Hospital in Boston. Identifying the role of BRAF made it possible for the first time to develop “a treatment concept for melanoma”, he says.

But it would be years before a promising drug became available. Jeff Sosman, a medical oncologist at Vanderbilt University Medical Center in Nashville, Tennessee, explains: “Until 2008, we honestly didn’t know if BRAF was targetable, and if by inhibiting this enzyme we would have an effective therapy,” he says. That year, clinics began testing a drug called vemurafenib (Zelboraf), which targets the mutant BRAF. About half of patients with advanced melanoma have a mutation in this protein,

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TREATMENT OF BRAF-MUTANT MELANOMA

Before 2011, few treatments were available for patients with advanced melanoma. Drugs gave a median survival of 8–9 months and only 15% of people lived for more than 3 years. But in the past four years, the US Food and Drug Administration has approved seven treatments that target the cancerous cells or trigger the immune system to do so, extending patients’ lives.

known as BRAF (V600E), and vemurafenib was their first chance at personalized medicine.

The results exceeded all expectations. Tumours regressed rapidly and some patients improved overnight. In 2010, a small phase I trial of vemurafenib showed complete or partial tumour regression in 26 of the 32 patients⁵. The response was greater than anything previously seen with advanced melanoma⁴. In a phase III study, Paul Chapman, a specialist in metastatic melanoma at the Memorial Sloan Kettering Cancer Center in New York, showed that after three months of vemurafenib therapy, patients with the BRAF (V600E) mutation were 74% less likely to die or see their cancer worsen than patients who received a standard chemotherapy agent⁶. And 48% of them saw the growth of their tumours shrink or stop.

The FDA fast-tracked the approval of vemurafenib for use in people with the BRAF (V600E) mutation in 2011, less than four months after it was submitted. A second BRAF inhibitor, called dabrafenib (Tafinlar), was given FDA approval in 2013.

FACING RESISTANCE

But cancer is a wily foe. Tumour cells mutate, and when a pathway is blocked, they find another route. So targeted therapies quickly lose their effectiveness, and many people who took vemurafenib found that resistance developed within six months. The tumours, which had once melted away, grew back with new mutations that were impervious to the drug⁷.

Other proteins in the same signalling pathway quickly became targets for drug discovery. BRAF inhibitors block the MAPK pathway, and scientists soon realized that most of the resistance comes from reactivation of the pathway through mutations in other genes that play a part in it⁷. The identification of these genes led to the development of more drugs that target the pathway, including MEK inhibitors, such as trametinib (Mekinist), which became the second major player in the treatment of advanced melanoma.

Oncologists then combined anti-BRAF and anti-MEK drugs with the aim of preventing the development of resistance. With the pathway effectively blocked at two points, the tumour cells struggled to develop new mutations. In

a small trial of the two drugs, Ribas and colleagues found that more than 85% of patients with a BRAF (V600) mutation who had never received a BRAF inhibitor responded to the combination of drugs, compared with only 15% of those who had developed BRAF resistance during an earlier treatment⁸. Patients who had never taken a BRAF inhibitor lived for 13.7 months before the disease progressed, compared with 2.8 months for those who had previously developed resistance to vemurafenib. In July 2014, GlaxoSmith-Kline stopped a combined phase III trial of trametinib and dabrafenib early because the drugs had obtained increased survival ahead of its target. “We now have two winning strategies,” says Caroline Robert, head of dermatology at the Institut Gustave-Roussy in Paris.

But *BRAF* is not the only important driver mutation in melanoma. Another mutation, in the *NRAS* gene, is found in approximately 20% of metastatic melanoma patients. Drug companies have struggled to find compounds that effectively target the mutated *NRAS* protein, however, so they have focused instead on the pathways *NRAS* activates, including MAPK. Indeed, says Sosman, inhibiting MAPK “is probably not enough, but it needs to be a component in the strategy”.

In July 2014, French researchers reported another mechanism of resistance to targeted therapies for melanoma⁹. They identified a cluster of proteins called eIF4F, which regulates protein synthesis. Tumours that respond to anti-BRAF drugs have low levels of eIF4F, and those that have developed resistance to these drugs have more. “Understanding this nexus is critical to overcoming resistance to cancer therapy,” says Robert, one of the study’s authors. The team has identified compounds that inhibit eIF4F and enhance the effectiveness of vemurafenib in mice with melanoma.

“It’s an interesting target downstream of many mechanisms of resistance to BRAF,” says Sosman, “and it’s exciting that a potential drug might be able to inhibit this effect.”

IMMUNE RESPONSE

Long before targeted therapies were possible, biomedical researchers had tried using the immune system to fight cancer. In the 1990s,

instead of applying an accelerator to the immune system, they tried lifting the brakes by blocking the action of a protein called CTLA-4, which keeps the immune system's T cells in check. CTLA-4 normally has a beneficial role in preventing the immune system from attacking normal tissue. But it is such an effective brake that it also stops T cells from destroying cancer cells. In 1996, a team led by James Allison, now at the University of Texas MD Anderson Cancer Center in Houston, showed that injecting mice with an antibody that blocks CTLA-4 could inhibit tumour growth¹⁰.

These findings eventually led to the development of the drug ipilimumab (Yervoy), a monoclonal antibody that acts as a 'checkpoint inhibitor' by binding to the CTLA-4 protein and stopping it from applying the brake. Ipilimumab was the first drug to extend the lives of patients with metastatic disease¹¹. In a large phase III trial of 676 patients with late-stage melanoma, those given ipilimumab survived on average for 10 months¹² — almost 4 months longer than those given another experimental treatment. The FDA approved ipilimumab for the treatment of metastatic melanoma in 2011.

In 2013, a follow-up analysis of 12 studies involving more than 1,800 patients given ipilimumab showed that 22% of patients survived for 3 years or longer, and some were approaching 10 years. Checkpoint inhibitors represent "a paradigm shift, probably the most important discovery in the field", says Ribas.

The trouble with ipilimumab is its toxicity. Releasing the brake on T cells enables them to attack not only cancer, but also normal cells in the skin, colon, endocrine system, eye and elsewhere, says Sosman, who conducted some of the ipilimumab studies. Using the drug requires vigilance from hospital staff to manage the side effects, and patients may be given steroids or even have the treatment discontinued, depending on the severity of the side effects.

Researchers have identified several other checkpoint inhibitors that also release the brake holding back T cells, but with less toxicity. Patients with metastatic melanoma often have high levels of a protein called PD-L1. When PD-L1 binds to a protein called PD-1, which is expressed on T cells, it allows cancer cells to hide from the immune system. Studies have shown that drugs that target these two proteins can shrink tumours.

Ribas and Robert recently led trials that used an antibody called pembrolizumab (also known as MK-3475) to target PD-1. The tumours shrank or disappeared in 52% of patients with metastatic melanoma who received the drug¹³. Another study¹⁴ found that pembrolizumab could slow tumour growth in patients who had stopped responding to drugs that target CTLA-4. Nearly 90% of those who responded to the drug saw their tumours shrink or disappear in six months.

"We see patients who have large, bulky

Scanning electron micrograph showing a blood vessel providing red blood cells (red) to a melanoma.

melanomas, tumours that two or three years ago if they said they didn't want to be treated, I would have said OK," says Ribas. "But with this antibody that releases the PD-1 brake, all of a sudden their tumours start melting away with limited side effects."

The FDA approved pembrolizumab (Keytruda) in September 2014. This is the first drug targeting PD-1 or PD-L1 to be approved in the United States, although Japan had already approved the anti-PD-1 drug nivolumab (Opdivo) in July. Anti-PD-1 drugs have been developed at a phenomenal speed, taking just three years from the first clinical trials to approval, says Ribas.

BETTER TOGETHER

Now that targeted drugs and immunotherapy have been established, the next development may be a combination of the two. Doctors can examine a tumour's biological traits and pick the best antibody or combination of drugs to attack it. For example, says Ribas, PD-L1 may be an important biological marker that will enable oncologists to identify patients who will respond best to pembrolizumab. In a large ongoing phase I study, almost half of the PD-L1-positive patients responded to pembrolizumab treatment, compared with only 13% of patients with PD-L1-negative tumours.

Drug companies are enthusiastic about immunotherapy because these drugs seem to be beneficial in several different types of cancer. Many of these checkpoint inhibitors are being tested in other cancers¹, including renal cell carcinoma, lymphomas, lung cancer and breast cancer. Although a smaller fraction of these patients respond to immunotherapy, the responses seem to last longer.

Ultimately, oncologists aim to combine the two treatments to produce a more potent effect. Using CTLA-4 and PD-1 inhibitors together could further boost T-cell activity by

releasing the brake at several points during the T cell's interaction with melanoma cells.

But combining targeted therapy with immune therapy might be even more powerful. Targeted drugs could wipe out one type of cancer cell and force it to adjust by developing new mutations. This would expose them to T cells that have had their brakes released to finish the job.

Today's therapies cannot help everyone with advanced melanoma, but physicians now have a choice of drugs to target different forms of melanoma, and researchers are developing the tools to match patients to specific treatments. "After more years of doom and gloom than I'd care to count, we've had this amazing trajectory that doesn't seem done yet," says Flaherty. "Our confidence keeps rising as our patients keep surviving." ■

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