MILLENNIUM PHARMACEUTICALS

Looking good: researchers are starting to see results in their search for improved drugs.

DRUGS

More shots on target

Drugs introduced to fight multiple myeloma in the past decade have revolutionized treatment and extended patients' lives. Are the improvements set to continue?

BY ADRIANNE APPEL

Multiple myeloma is a confounding disease to treat. More often than not, treatment seems to be effective, only for the blood malignancy to come roaring back months or years later. Most patients go through four, five or even more rounds of potent drug treatment in their struggle against mounting myeloma cells and increasing drug side effects.

But two classes of drug that became available in the past decade — proteasome inhibitors and immunomodulators — have been far more effective than any previous drugs against this form of cancer. Just three of these new drugs have so far been licensed — a proteasome inhibitor called bortezomib and two immunomodulatory drugs, thalidomide and its cousin lenalidomide — with additional drugs currently in clinical trials.

In the 1990s, the median survival time of patients whose only option was conventional chemotherapy was just three years. The new drugs extended this to five years. Furthermore, "90% of patients respond, while it used to be 65%," says haematological oncologist Keith Stewart of the Mayo Clinic in Scottsdale, Arizona. "They get immediate pain relief. They get into remission faster and they stay in remission longer." More people with multiple myeloma, especially those under 65 years of age, can expect to live 10 years or more with the disease, he says. These younger patients generally receive bortezomib intravenously, often as a first treatment in a two- or three-drug combination with a conventional chemotherapy drug, a strategy based on research showing that hitting myeloma early and hard gives a better chance of remission. Younger patients can also undergo autologous stem-cell transplants in a bid to get them into remission (see 'Transplants on trial', page S46).

Patients aged 70 and older in the United States, or 65 and older in Europe, are ineligible for stem-cell transplants and are often too fragile to tolerate intravenous drugs. Their treatments are focused on oral drugs such as thalidomide and lenalidomide, as well as conventional chemotherapy. But the myeloma nearly always returns after several months or years, requiring another round of drugs. Each time the cancer comes back, the treatment options are further narrowed, as the myeloma cells develop resistance to more of the available drugs.

PROTEASOME INHIBITORS

The development of bortezomib sprang directly from basic research on the cell and has helped build the multi-lane research highway that has now delivered several second-generation proteasome inhibitors to clinical trials.

In multiple myeloma, plasma cells reproduce furiously, creating piles of damaged proteins that must be cleared from the cell. Protein complexes called proteasomes normally remove them, aided by enzymes that slice up the amino-acid chains. But in myeloma cells, this proteasome,

known as 26S, can barely keep up with demand, suggesting a weakness that could be exploited. In 1993, Alfred Goldberg, a cell biologist at Harvard Medical School in Boston, Massachusetts, created the first proteasome inhibitor, MG132. It worked by interfering with protein clearing. Myeloma cells, which are already awash with damaged proteins, proved particularly vulnerable to MG132 and would suffocate in their own waste protein. Further refinement of MG132 led to bortezomib and the other proteasome inhibitors now in development.

Early trials of bortezomib hinted at its effectiveness, particularly against myeloma cells that were already resistant to conventional chemotherapy. The drug demonstrated "remarkable activity against myeloma in a phase I trial", recalls Kenneth Anderson, director of the haematologic neoplasias division at Harvard Medical School in Boston, Massachusetts. When his phase II trial showed bortezomib to be twice as effective as the standard therapy for multiple myeloma, he successfully petitioned the US Food and Drug Administration (FDA) in 2003 for fast-track approval to use it on patients who had exhausted other possible treatments. In 2008, bortezomib (marketed as Velcade by Millennium Pharmaceuticals of Cambridge, Massachusetts) became the standard drug to treat multiple myeloma.

But bortezomib has some serious side effects. It often causes severe nausea, and can aggravate and cause problems in the heart, lungs and kidneys. It can also induce pain or tingling in the feet and hands. More than 40% of patients are afflicted with this peripheral neuropathy, and 13% are debilitated by the symptoms. So onerous are these side effects that many patients give up on the drug before completing a full course. The neuropathy is probably associated with bortezomib's sloppy mechanism. Although it is intended to target a particular enzyme called the chymotrypsin-like protease enzyme, it can also disrupt the proteasome's two other enzymes. And as with other drugs for multiple myeloma, nearly all patients develop resistance to bortezomib.

Alternative proteasome inhibitors are already in clinical trials, and one — carfilzomib — is nearing approval. Developed by Onyx Pharmaceuticals of South San Francisco, California, carfilzomib is now in phase III trials. It works in much the same way as bortezomib, but has one clear advantage: fewer than 1% of patients experience neuropathy. Like bortezomib, carfilzomib acts on the chymotrypsin-like protease enzyme, but it is more selective than bortezomib and doesn't hit the 26S proteasome's other two enzymes. It should soon receive FDA approval for use by patients who have become resistant to bortezomib and lenalidomide, Stewart says.

Another next-generation proteasome inhibitor — MLN9708, developed by Millennium Pharmaceuticals — also shows a low association with neuropathy, probably because it accurately targets the chymotrypsin-like enzyme. Now in phase I and phase II trials for relapsed patients and in combination with other drugs for newly diagnosed patients, MLN9708 is "very effective in overcoming bortezomib resistance", says Anderson, whose lab is investigating the drug. Unlike the other proteasome inhibitors, MLN9708 can be taken orally. Anderson's lab is also working with NPI-0052, which was developed by Nereus Pharmaceuticals in San Diego, California, and is now in phase I trials. This drug hits not just one but all three inhibitors of the 26S proteasome, and easily overcomes bortezomib resistance. But it also gives patients a powerful dose of side effects, Anderson warns.

Other promising drugs include the oral proteasome inhibitor ONX 0912, which is being tested against solid tumours in phase I trials. A phase II trial in patients with multiple myeloma and other blood cancers will begin soon, according to the drug's developer, Onyx Pharmaceuticals. Another drug, CEP-18770, developed by Cephalon in Frazer, Pennsylvania, works in a similar way to bortezomib, and has about the same efficacy against multiple myeloma — but with less toxicity.

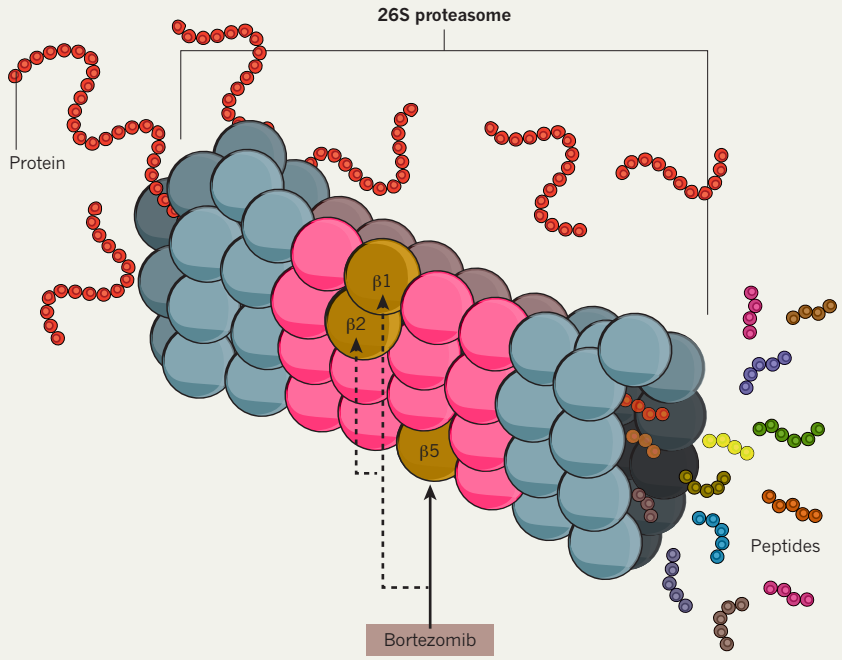
THE IMMUNOMODULATORS

From an unlikely start, a new category of drugs — the immunomodulators — has opened up fresh treatment options in multiple myeloma. The sedative thalidomide became notorious in the 1960s when it was linked to birth defects in babies whose mothers had taken the drug while pregnant. But since the 1990s, thalidomide has found new roles, first as a treatment for leprosy and, since 2006, as a drug to treat multiple myeloma. Lenalidomide, a derivative of thalidomide and also approved in 2006 for use in multiple myeloma, is now preferred over thalidomide because it is less likely to cause peripheral neuropathy. Both thalidomide and lenalidomide (marketed as Thalomid and Revlamid, respectively, by Celgene of Summit, New Jersey) fight multiple myeloma by reducing levels of cytokines, including the interleukin-6 (IL-6) protein. Because IL-6 helps malignant myeloma cells survive by inhibiting apoptosis (cell death), any drug that lowers IL-6 levels will diminish the cancer.

Thalidomide is approved for use in newly diagnosed patients, and is favoured for older patients who cope best with oral drugs. Lenalidomide is licensed for use in combination with the anti-inflammatory dexamethasone in patients who have previously been treated with other drugs, and is also used in newly diagnosed patients. For younger patients, adding bortezomib to the mix increases the benefit of lenalidomide: one 2010 study showed an almost 100% positive response to this combination by patients in an early stage of the disease, says Anderson, whose lab oversaw the trial. Even in advanced myeloma patients, 58% responded to the triple-drug therapy. Studies also are underway to test lenalidomide as a maintenance drug that relatively healthy

DISRUPTING A PROTEIN DISPOSAL OPERATION

Proteasome inhibitors such as bortezomib turn off the machinery that disposes of damaged proteins, causing myeloma cells to suffocate in their own waste. The drug targets the β5 (chymotrypsin-like) enzyme but also hits the β1 and β2 enzymes, causing side effects.



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THE ECSTASY ALTERNATIVE

A notorious party drug aims to beat myeloma.

ARCLIGHT/ALAMY

Immunologist John Gordon is trying to turn the illegal street drug MDMA — also known as ecstasy, E or X — into a cancer therapy.

This isn't such a crazy idea. More than ten years ago, Gordon's team at the University of Birmingham, UK, discovered that cells in the immune system have transporters for taking up the neurotransmitters serotonin and dopamine, just like cells in the brain and central nervous system. They also found that these transporters allow some antidepressant drugs and MDMA (3,4-methylenedioxymethamphetamine) to enter.

Why can cells in the immune system do this? It's not something Gordon had considered until about ten years ago when it came up in discussions with his colleague Nicholas Barnes, a neuropharmacologist at Birmingham who studies serotonin. At the time, Gordon was investigating whether there was a relationship between brain neurochemicals and the combative attitude of cancer patients who beat their disease — a psychological state probably influenced by serotonin. Conversations between Gordon and Barnes led to a fresh line of enquiry about the immune system, brain chemicals and possible new cancer treatments.

The team knew they were on to something when they mixed serotonin in a test-tube with Burkitt's lymphoma cells, a type of B-cell cancer strongly associated with AIDS. Many of the cancer cells died: the serotonin had entered the cancerous immune cells and killed them. Gordon and Barnes speculated about the transport system for serotonin in immune-system cells, and wondered whether it could be exploited to deliver lethal levels of mood-altering drugs into cancers, particularly immune-cell cancers such as lymphoma, leukaemia and multiple myeloma.

"That's how we got to where we are," Gordon says. "It's not something that I alone would even begin to study, because — why would you?" The team tried using fluoxetine (Prozac), a selective serotonin reuptake inhibitor, against lymphoma B cells, with promising results. But because fluoxetine is a generic drug, no drug company stepped forward to further the research, Gordon says.

So Gordon switched to MDMA. Preliminary tests are encouraging, and the team, joined by pharmacologist Matthew Piggott of the University of Western Australia in Crawley, is now creating analogues to MDMA that are more potent cancer killers but are safe enough to be ingested. The idea is to limit the drug's neurotoxicity, and therefore its psychotropic activity, while increasing its anticancer action. At levels typically found in the street drug, "to kill the lymphoma you'd have to kill the patient", Gordon says.

Gordon modified the alpha-carbon site of MDMA by adding lipophilic aromatic rings, magnifying MDMA's cancer-killing potency 100-fold. This alteration also decreases MDMA's psychoactive affect, he reported in a paper published in August 2011. "As we add more aromatic rings, we see improved killing," he says. This effect suggests that the lipophilicity enhances the drug's ability to cross the cell membrane, allowing more of the drug to enter the cell.

Gordon estimates that his approach is at least five years away from preclinical testing. "We'll try a few more variants, and once we're pretty confident we have the optimal compound, that's when we'll go ahead," he says. By this point, Gordon believes, the cancer-killing MDMA analogues will have little psychoactive capacity left. **A.A.**

patients can take to keep their myeloma at bay.

But lenalidomide's future as a myeloma therapy is in question. A safety warning from the FDA in April 2011 cited studies showing an association between the drug and the later development of secondary cancers — a particular concern when treating younger patients. "It's a big problem for us," says haematologist Vincent Rajkumar of the Mayo Clinic in Rochester, Minnesota. "Secondary cancers can be devastating and we really need to know if overall survival is superior after taking lenalidomide."

The next generation of immunomodulatory drugs could mitigate these fears. Early trials at the Mayo Clinic suggested that pomalidomide was a safe and effective alternative for patients who develop resistance to lenalidomide and bortezomib. Two phase III trials of pomalidomide — being developed by Celgene as Actimid — are currently underway. The Nimbus trial will enrol 400 patients to study whether pomalidomide plus dexamethasone is more effective than dexamethasone alone in resistant patients. A sister trial will give pomalidomide alone to 85 people who failed to respond to the dexamethasone control in Nimbus. These trials will lay the groundwork for an application to the FDA to use pomalidomide in newly diagnosed patients. The drug is "enlarging treatment opportunities", says Antonio Palumbo, a haematologist at the University of Torino in Italy.

SUPPLANTING TRANSPLANTS

Some of the treatments being developed for multiple myeloma seem to be nearly as effective as stem-cell transplants, which are offered to younger patients as a highly effective but brutal treatment. Anderson says that many patients ask him if they really have to endure the gruelling procedure if today's drugs are almost as good.

The answer, Anderson says, is still yes, because most patients become resistant to medication, even though the drugs are getting better all the time. A combination of lenalidomide, bortezomib and dexamethasone was recently tested against stem-cell transplants in a 1,000-patient study in France. The trial showed equivalent response rates and better progression-free survival for the combination therapy than for the transplants, and has inspired a similar US trial, led by Anderson's lab.

The past decade's progress in developing drugs for multiple myeloma has led some to hope that this form of cancer will succumb to treatment in the not too distant future, as new proteasome inhibitors and immunomodulatory agents become available. Thanks largely to these drugs, says Stewart, "for many patients, multiple myeloma has become a chronic condition rather than a quickly fatal disease". ■

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