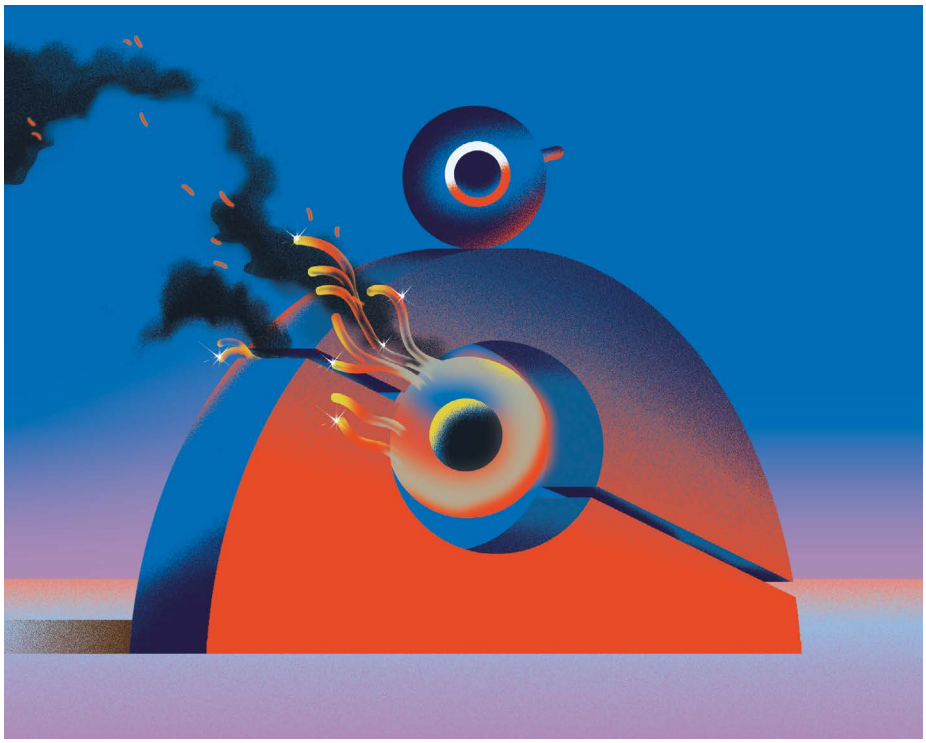

SANDRO RYBAK FOR *NATURE*

Burning questions about smouldering myeloma

Researchers are amassing evidence about the best ways to treat myeloma before it develops into active disease. **By Sarah DeWeerdt**

Early detection is a cherished goal of researchers working on most forms of cancer. But when it comes to multiple myeloma, early detection presents a problem. "Myeloma is one of those few diseases which does have a precursor state," says Noopur Raje, director of the multiple myeloma programme at Massachusetts General Hospital in Boston. Or, more precisely, two precursor states: monoclonal gammopathy of undetermined significance (MGUS) and smouldering myeloma.

But screening isn't recommended for the earlier and less serious MGUS, or for the more-advanced smouldering myeloma. And there's no approved treatment for either condition. If they are detected, the standard management is to simply monitor a person until they progress to full-blown, or active, disease, which does not always happen.

Both MGUS and smouldering myeloma are characterized by the presence of abnormal plasma cells in the bone marrow and of monoclonal protein, an abnormal protein produced by these cells, in the blood, but people with either precursor condition are asymptomatic. Active myeloma, in turn, is conventionally defined by the presence of a set of symptoms known as CRAB signs: elevated calcium in the blood, renal damage, anaemia and bone lesions. These all indicate damage to various body systems.

For other cancers, potentially cancerous tissue can be removed, but this is not possible for myeloma. So myeloma is one of the few cancers that physicians don't try to treat early, when its effects are still localized. That lack of early treatment might explain why myeloma has conventionally been very difficult to cure, says Elisabet Manasanch, a myeloma specialist at the University of Texas MD Anderson Cancer Center in Houston.

But that might be about to change. Researchers are homing in on an understanding of which people with myeloma precursors are likely to progress to active disease. And they are amassing evidence about the best ways to treat myeloma when it is at the smouldering stage. These advances are raising hope that early detection could lead to early treatment, opening up the possibility of increased survival.

Precursor parallels

Myeloma's earliest precursor, MGUS, is usually found by chance, when tests for other health concerns identify the presence of monoclonal protein in a person's blood. In people with MGUS, the monoclonal protein is present at relatively low levels and less than 10% of their bone marrow is made up of abnormal plasma cells.

Multiple myeloma is nearly always proceeded by MGUS. About 3% of people over the age of 50 have MGUS, and, on average, 1% of people with MGUS progress to multiple myeloma each year. But people with MGUS can live for many years without developing myeloma, says Ronald Go, a haematologist at the Mayo Clinic in Rochester, Minnesota. "Most never progress," he adds.

Smouldering myeloma was first described[1] in 1980, when six people were found to have enough monoclonal protein in their blood and abnormal plasma cells in their bone marrow to suggest that they had myeloma. But they did not have myeloma symptoms, even after 5 years of follow-up. Like MGUS, smouldering myeloma is asymptomatic. But people with the precursor condition have higher levels of monoclonal protein in their blood than do those with MGUS, more abnormal plasma cells in their bone marrow (at least 10%) or both.

Treating myeloma at the smouldering stage has long been a tantalizing prospect. In the past, however, myeloma treatments were so demanding and toxic – high-dose chemotherapy followed by an infusion of the person's own stem cells, for example – that they were difficult to justify in people who didn't have symptoms and might never develop them. Evidence also suggested that treatment provided little benefit.

But in the early 2000s, the advent of proteasome inhibitors, such as bortezomib, and immune-modulating imide drugs, such as lenalidomide, began to change the calculus. These drugs were much easier for people to tolerate than conventional chemotherapy. And they were also more effective, often resulting in temporary remission for people with active myeloma. Thanks to these advances, says Raje, "one could begin to ask the question: can we change the natural history of this otherwise incurable cancer?".

The advent of these drugs posed the question: who should be treated early? Some cases of smouldering myeloma behave much like MGUS and might never progress to active disease, whereas others progress within a couple of years of diagnosis.

"You don't want to overtreat too many people and cause harm," says Irene Ghobrial, an oncologist at Dana-Farber Cancer Institute in Boston, Massachusetts. These treatments, although gentler, still have side effects and might increase the risk of certain other cancers. They're also extremely expensive. But, "you don't want to undertreat people and cause clonal selection", Ghobrial says, referring to the process of eliminating the less aggressive myeloma cells and enabling the more aggressive ones to take over.

This conundrum has spurred efforts to find ways to sort people with smouldering myeloma into risk categories. In 2014, the definition of active myeloma was broadened to include people without symptoms but with certain biomarkers that meant they had an 80% risk of developing symptoms within two years. This shifted 10–15% of people with smouldering myeloma to an active disease status, and resulted in them receiving immediate treatment.

For those people still considered to have smouldering disease, however, the goal of determining meaningful high-, medium- and low-risk categories has been more elusive. Several systems have been proposed that can define groups of people with smouldering myeloma that differ in their average time to progression to active disease. But different models don't always include the same people in their high-risk categories. And people at high risk still include many whose disease will progress slowly, if at all – raising the question of whether they should receive treatment.

To refine the risk categories, researchers are investigating genetic abnormalities in myeloma cells. Certain chromosomal abnormalities have been linked to an increased risk of progression. A sequencing study by Ghobrial's team found a handful of mutations affecting DNA-repair mechanisms or the mitogen-activated protein kinase pathway, a signalling pathway implicated in cancer, that are associated with higher risk of progression[2]. Other factors are also likely to affect the risk of progression: chiefly, the bone-marrow microenvironment that surrounds malignant plasma cells and the immune regulation mechanisms that determine whether the body can hold the population of abnormal plasma cells in check.

"The line is very fine" between high-risk smouldering myeloma and active disease, says María-Victoria Mateos, a haematologist at the University of Salamanca in Spain. "In fact, the future will be to continue incorporating smouldering myeloma with an imminent risk of progression into the definition of myeloma."

Raje carries this thought to its logical, if radical, conclusion: "We need to get rid of this whole definition of smouldering myeloma." People with abnormal plasma cells judged to have a low risk of progression to active myeloma could be monitored. But those at high risk of progression should be treated, "as you would treat full-blown myeloma, because that's your chance of cure", Raje says.

Trial treatments

For now, there's no approved treatment for smouldering myeloma. But evidence suggests that treatment at this stage can delay progression or increase survival time, making defining risk categories all the more urgent. Ongoing trials are testing a variety of treatment strategies in people with smouldering disease.

One possibility is to treat smouldering myeloma in the same way as active disease – just earlier. Another idea is that it might be possible to stop myeloma progressing from the smouldering stage using the same drugs that are used to treat active disease but in a simpler, less aggressive way. Researchers led by Mateos reported that people with high-risk smouldering myeloma treated with the immune-modulating drug lenalidomide and dexamethasone, a steroid commonly used in myeloma treatment, fared better than those who received standard monitoring[3]. The treatment delayed progression of myeloma and improved overall survival. These benefits are still seen after a median follow-up of 11 years, Mateos says.

> **"We need to get rid of this whole definition of smouldering myeloma."**

Another large trial of 182 people tested lenalidomide in people with smouldering myeloma in all risk categories[4]. People who received the drug were 72% less likely to progress to active myeloma over the course of the study than were those who received the standard watch-and-wait care.

These two trials, both phase III, are widely seen as providing proof of concept for treating smouldering myeloma. But both have limitations. The first trial included some people who would currently be classified as having active myeloma. And the second did not demonstrate an overall survival benefit, which some researchers say is necessary to demonstrate that a treatment can truly alter the course of the disease.

A third approach is to develop treatments specifically for smouldering myeloma, rather than borrowing drugs used for the active disease. If researchers can work out the mechanisms that underlie the switch from smouldering to active disease, they could intervene to block them. Both Manasanch and Raje are conducting studies of vaccines with this goal in mind.

The prospect of effective treatment for smouldering myeloma raises the question of whether physicians should look for myeloma precursors more systematically. Until now, this idea has been controversial. For those with known MGUS, guidelines generally advise a blood test every year to gauge whether MGUS is progressing, but there's little evidence that this monitoring improves outcomes. And because MGUS is so common, identifying the millions of people who have it and carrying out yearly blood tests would be a major drain on haematologists' time, and a financial strain on health-care systems. The diagnosis can also be a psychological burden, Go says.

Nevertheless, a better understanding of who is likely to progress to active disease could justify looking for people with myeloma precursor conditions. To gauge the feasibility, usefulness and unintended consequences of screening, Ghobrial is working on the PROMISE study, a US$10-million effort to screen 30,000 people in the United States at elevated risk of myeloma – particularly, African Americans and people who have a family member with the disease – for signs of MGUS and smouldering myeloma.

In Iceland, the iStopMM study will screen and monitor 80,000 people – around half the country's over-40 population – for myeloma precursors. So far, it has tested blood from almost 70,000 participants, and identified 2,200 cases of MGUS and 130 of smouldering myeloma, says Sigurdur Kristinsson, a haematologist at the University of Iceland in Reykjavik, who heads the effort. The preliminary data suggest that smouldering myeloma is more common than previously thought. This adds to the urgency of determining who should be screened for multiple myeloma precursors and how often, Kristinsson argues. Without screening, "you won't find them. And if you won't find them, how can you treat them?" he says. "So that's sort of the dilemma here."

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