Breakthrough drug shows early promise for multiple myeloma

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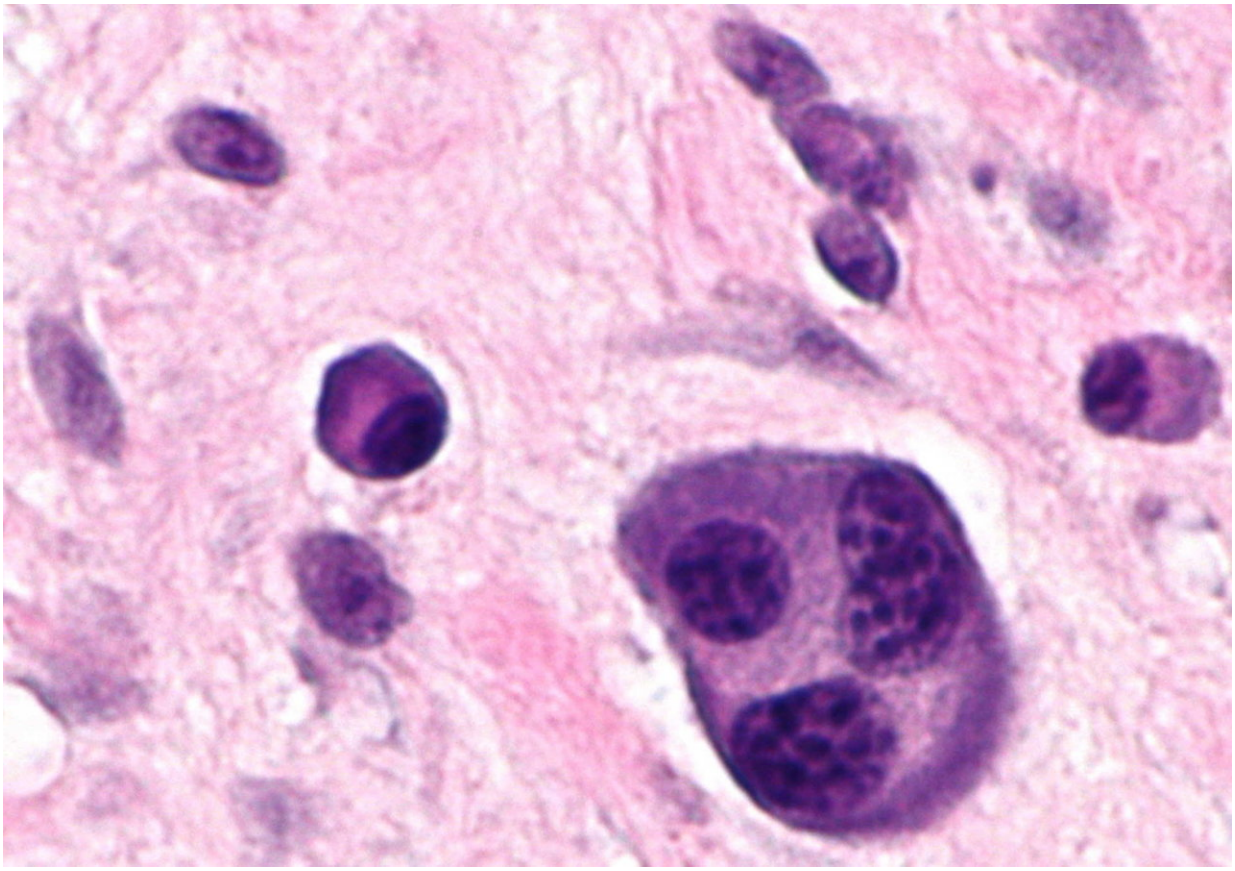

Multiple myeloma affects the bone marrow, causing abnormal plasma cells (pictured) to build up and cause tumours around the body. Credit: Wikicommons/Nephron

A small clinical trial has shown that a new drug has promise for targeting

tumours in patients with an aggressive type of blood cancer.

Multiple myeloma is a relatively rare type of cancer that develops in the bone marrow – the spongey tissue inside the bone where new blood cells are produced – often spreading to multiple sites within the body.

Along with aching and exhaustion, patients can suffer from brittle bones which break easily and even cause fractures in their spine.

Its insidious nature makes it difficult to tackle with standard treatments, and a poor prognosis for patients with aggressive forms of the disease means that more effective treatments are needed.

Now a small, early-stage clinical trial involving three patients, has shown the first clinical evidence of an unlicensed drug selectively killing myeloma cells in the marrow, while leaving the healthy tissue of the patients untouched.

The researchers, led by a team at Imperial College London, are cautious to speculate, but say if the initial results can be replicated in larger trials then the treatment has the potential to improve patient outcomes.

"Our findings show that this compound could work for some patients with this aggressive form of cancer," said Professor Guido Franzoso, Chair of Inflammation and Signal Transduction in the Department of Medicine, who led the research. "Although we were only able to follow up the patients over a short period, this is the first clinical evidence that our compound can specifically target cancer cells in patients, whilst demonstrating no sign of toxicity."

Myeloma typically occurs in older adults (over 60) and the disease is more prevalent in men than women. More than 5,500 cases of the condition are diagnosed every year in the UK, but while outcomes have

improved in recent years, the disease cannot be cured in most patients.

Patients are generally treated with a combination of chemotherapy, steroids and so-called 'novel agents' that target general biological processes which keep myeloma cells alive and make them spread throughout the body, but are also needed for the normal function of healthy cells.

"We can now keep the disease under control for several years in most cases, but ultimately we almost always run out of treatment options," explained Dr. Holger Auner, a Clinical Senior Lecturer at Imperial and Consultant in Haematology, who was involved in the study. "While the findings of this pilot study must be interpreted with caution at such an early stage of clinical testing, they are nevertheless highly encouraging and strongly support the further development of this approach."

At the heart of myeloma is a rogue signalling process, which causes cells in the bone marrow to replicate uncontrollably. The key is NF-κB, a transcription factor which binds to DNA, affecting the activity of genes involved in cell survival and inflammation.

For the past 30 years the pharmaceutical industry has worked aggressively to develop drugs to block the NF-κB pathway, with the hope of treating an array of cancers and inflammatory diseases.

Despite the huge investments in R&D, they have had little success. Hundreds of drug candidates designed to block the pathway have failed to make it through the development pipeline – either from their ineffectiveness or, more commonly, having severe unwanted side effects or being toxic to healthy cells and tissues.

A new way of tackling the disease

Professor Franzoso's team took a different approach. Rather than looking to block the entire pathway, they broke it down into bite-sized chunks to focus on its individual components. Their early work uncovered a drug target made up of two parts – a protein called GADD45b and the MKK7 enzyme – which, when bound together, block the genetic instructions which tell a cell to commit suicide. This process, which is called apoptosis, is an important biological mechanism to stop cells from becoming cancerous and then spreading, where the cells 'sense' that they are abnormal and commit cellular suicide as a result.

"We developed a drug that could block this signalling mechanism in cancers, but not in normal cells," said Professor Franzoso. "The study showed it worked as effectively as other drugs commonly used to treat patients, killing myeloma cells in laboratory tests and in mice; but unlike existing drugs, it had no toxicity and no detectable side effects."

The compound, called DTP3, targets the GADD45b–MKK7 complex, stopping the two from joining and so disrupting their action, ultimately causing cells to self-terminate.

Encouraging results

The latest findings, published in the *British Journal of Haematology*, provide the first evidence that the same mechanism seen in the lab also works in patients with multiple myeloma. According to the researchers, these early-stage clinical data suggest that the drug may be safe and effective for human use.

In a pilot trial, three patients with progressive forms of advanced multiple myeloma were administered the treatment in the clinic. During the trial, patients received increasing doses of the drug intravenously, three-times a week.

After a round of treatment (a total of 28 days), two of the three patients showed that the drug was able to activate the cell-suicide mechanism in myeloma cells, but crucially, not in their healthy cells. In one of the two patients, who had been treated with a higher dose of the drug, myeloma progression was halted for three months. Importantly, none of the three patients demonstrated any sign of toxicity or any unwanted side effects from the drug.

While the analyses of blood and bone marrow cells from two patients revealed all the hallmarks of apoptosis – showing that the drug had the same action as in the pre-clinical trials – the third patient showed no sign of apoptosis in myeloma cells, indicating that the tumour was not responding to the treatment.

According to Professor Franzoso, the lack of effect in the third patient is likely due to subtle genetic differences in the tumour. One possible explanation, could be an inactivity of the GADD45B gene, which contains the genetic instructions for making the GADD45b protein. Early analyses suggest the gene is 'switched on' only in the myeloma cells from the two patients who responded to the drug, but not in those from the third patient.

The researchers believe that the activity of the GADD45B gene could be used in the future as a biomarker to identify those patients whose tumours are likely to respond to treatment.

"Multiple myeloma is a disease with a complex genetic basis," explains Professor Franzoso. "GADD45b is not expressed or 'switched on' in all myeloma cells, and so it's the best biomarker we have at the moment. In the future, we may also have other biomarkers which could help us to predict which patients might respond to treatment."

The researchers stress that while the clinical results from this initial trial

are highly encouraging, more work is needed to determine if the drug could be an effective treatment for patients with multiple myeloma.

"We have shown that this drug can work as expected from the pre-clinical studies, but so far we have only tested it in a small number of patients and only at relatively low doses," explained Professor Franzoso.

"In the future, we hope to be able to conduct larger trials to establish whether the drug could be used in the clinic to benefit patients with multiple myeloma, but an effective new drug treatment may still be a few years away."

More information: Laura Tornatore et al. Clinical proof of concept for a safe and effective NF-κB-targeting strategy in multiple myeloma, *British Journal of Haematology* (2018). DOI: 10.1111/bjh.15569

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