

Battling blood cancer: virus targets multiple myeloma

A successful treatment for the bone marrow cancer, multiple myeloma, has so far remained elusive. Pioneering research led by **Dr Eric Bartee**, of the Medical University of South Carolina, suggests a two-pronged approach to improving myeloma recovery rates, using a virus that is only harmful to rabbits.

Multiple myeloma (or simply 'myeloma') is one of the most common blood cancers – making up 10–15% of cases and affecting some 24,000 new patients each year. Multiple myeloma affects the white blood cells known as plasma cells, which are produced in the bone marrow, and is typically found at multiple sites such as the spine, skull, pelvis and ribs. Symptoms can include bone pain and fractures as well as anaemia and, ultimately, it can result in death.

A LIFE SENTENCE

The progression of multiple myeloma under current treatment practices tends to follow a pattern of remissions and relapses, with only one-third of patients surviving more than ten years after diagnosis. Standard treatment for the disease involves repeated cycles of chemotherapy, to destroy myeloma cells in the body, followed by transplantation of replacement stem cells to enable the body to make healthy plasma cells. The transplant usually comprises of cells taken from the patient's own blood stream prior to the chemotherapy – and hence is known as an 'autologous' stem cell transplant.

Autologous stem cell transplants have vastly improved remission rates and survival times compared to chemotherapy alone, but sadly the majority of patients will ultimately

relapse. The prognosis for these relapsed patients, says Dr Bartee, is 'grim'.

HIDDEN AWAY

There are two possible reasons for the return of cancer symptoms in multiple myeloma patients treated with autologous stem cell transplants. The most likely explanation is that small numbers of myeloma cells survive chemotherapy in inaccessible parts of the bone marrow, and can then re-emerge, multiply and spread. However, a second cause may also contribute: accidental contamination of the stem cell transplant with small numbers of myeloma cells circulating in the blood stream. These again can multiply and spread once transplanted into the body.

Dr Bartee's work focuses on eliminating both these sources of myeloma cells, in the hope of developing a treatment that will prevent relapse and improve survival rates for patients with multiple myeloma.

AN UNLIKELY CHAMPION

The unusual tool that Dr Bartee and colleagues are using in their research is a pathogenic virus related to smallpox and known as 'myxoma'. This virus is the cause of the notorious 'myxomatosis' disease that has been used in many countries as a biological control agent against rabbits. Myxoma was recently discovered to belong to a group of

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viruses known to target and kill cancer cells – the so-called ‘oncolytic’ viruses.

Dr Bartee believes that the myxoma virus can be used to seek out and destroy myeloma cells – both within the body and in the stem cell transplants – before they are reintroduced to the patient. This offers two complementary avenues to improving clinical outcomes for myeloma patients.

Unlike other viruses that have been tested as oncolytics, the myxoma virus should be completely safe, since it does not cause disease in any organism other than rabbits. It therefore poses no risk to the patient or the wider human population. It also avoids the problem – found with many oncolytic viruses such as measles – that the patient’s own immune system recognises and eliminates the virus due to previous vaccination or infection.

FRONTLINE THERAPY

Using laboratory mice as a model, Dr Bartee’s team has shown that the myxoma virus can distinguish between normal and cancerous cells, eliminating up to 90% of myeloma cells within 24 hours after treatment. The myxoma virus does this via two mechanisms. Firstly, in all mice tested, some myeloma cells were killed by direct contact with the myxoma virus particles. This rapidly induced a process of programmed cell death known as ‘apoptosis’. Although this translated into minimal increases in survival for the mice, Dr Bartee believes that it might have significant

The myxoma virus has the potential to become a versatile tool in the battle against multiple myeloma

clinical potential when combined with other treatments such as chemotherapy.

Remarkably, however, in a quarter of the mice, complete eradication of the myeloma cells was achieved. This occurred through a second mechanism, in which the virus induced the mouse’s own immune system to attack the cancer cells.

PROGRESS WITH ‘PURGING’

Dr Bartee’s lab is currently exploring whether the myxoma virus can be harnessed for use directly in multiple myeloma patients before, after, or in combination with existing chemotherapy drugs. However, the prospect of using myxoma in this way remains a long way off. For a start, unlike many other viruses, myxoma has not previously been used in humans, so a lot of work needs to be done to develop safe, clean and consistent stocks of the virus before clinical trials can begin.

The second approach to using myxoma is

Q&A

How was the myxoma virus’ ability to destroy cancer cells discovered?

The initial discovery was actually made by my post-doctoral mentor Dr Grant McFadden. He had been studying the myxoma virus for many years with the goal of understanding the basic biology of viral infection. As part of this work, he was interested in understanding why the virus could infect rabbits but not humans or mice. The ability of any virus to infect a host is determined by a complex tug of war between the host’s anti-viral defences (in this case a pathway known as the interferon system) and the virus’s counter measures to these defences. Grant eventually found that myxoma induced a robust interferon response in all species. Myxoma’s countermeasures to interferon, however, only worked in rabbits. Therefore in all other species, the virus lost the tug of war. It has long been known, however, that the interferon system frequently doesn’t work correctly in human cancers. Therefore, Grant hypothesised that if myxoma virus was placed directly into a tumour, the host’s interferon system would be incapable of stopping the virus as long as it stayed in the tumour. Turns out he was right.

What hurdles need to be overcome before the myxoma virus can be used directly to treat myeloma patients?

While there are likely some additional experiments which should be done, the primary hurdle is to generate a virus of sufficient purity to use in humans. For traditional drugs, this is a relatively straight

further advanced towards clinical application. This method involves using the virus to decontaminate autologous stem cell samples prior to transplant into patients. The technique, termed ‘purging’, prevents reintroduction of any myeloma cells along with the vital blood-cell-producing stem cells.

Using laboratory populations of human myeloma cells, Dr Bartee and colleagues have successfully shown – for the first time – that treatment with myxoma virus particles results in the rapid and complete death of myeloma cells, while completely sparing healthy blood-

forward process. However, for viruses it is much more complex since the virus must be grown in living cells: after the virus is made, it must be purified away from the cells used to grow it before it can be used in patients. This is a very difficult and expensive process.

How does an autologous stem cell transplant work?

Stem cell transplants are used in combination with a procedure known as myelo-ablative chemotherapy. Myelo-ablative chemo is basically treatment with *really* high doses of normal chemo drugs. This is more effective at killing tumour cells since you are using more of the drug. However, it comes at the cost of significantly increased toxicities. In the context of myelo-ablative therapy, the toxicity which is most concerning is the elimination of a patient’s hematopoietic stem cells (the cells which constantly produce new blood for the patient). Since you always need new blood to survive, myelo-ablative therapy by itself is actually lethal. To survive the procedure, it must therefore be combined with some method to replace the hematopoietic stem cells which were killed. Autologous transplant does this by removing a patient’s own hematopoietic stem cells before the myelo-ablative therapy is given and then giving these same cells back to the patient after the myelo-ablative therapy is finished. This has the advantage of being safe and easy; however, since the hematopoietic stem cells must be removed prior to treatment, the patient still has cancer when they are taken out. This unfortunately means that the blood or bone marrow where the hematopoietic stem cells

producing stem cells. When samples treated with myxoma were transplanted into mice, the mice remained healthy and no myeloma cells were detected in their bodies. This suggests that the myxoma virus fully and effectively purged the samples of cancerous cells.

Treatment of autologous stem cell transplants with myxoma virus is a quick and easy process, making it an attractive strategy for improving outcomes of myeloma treatment. Unusually, myxoma is a virus that does not need to complete its life cycle and replicate itself to cause the death of host cells. Therefore, it

reside often contains trace amounts of cancerous cells which are then given back to the patient during the transplant.

Are the two methods of treatment using myxoma mutually exclusive, or might benefits be obtained from using both?

We have not examined this specifically; however, they should absolutely be able to be combined. The treatment of myeloma which already exists within the patient (residual disease) is done by simply injecting large amounts of the virus into the blood stream. One of the beauties of the purging strategy is that the virus used to treat the autologous transplant sample never has to be washed away. You simply have to add it to the transplant sample, wait a few minutes for the virus to find and bind to the myeloma cells (10–15 mins is typically enough time in our studies) and then proceed with the transplant as normal. This means that any virus which does not bind to a myeloma cell ends up being injected directly into the blood stream, effectively mimicking the treatment that we demonstrated was effective against residual disease. We actually have some anecdotal evidence that using the virus as a purging agent during autologous transplant might make the treatment of residual disease better since the virus can bind to cells found in the transplant sample and use those cells as carriers to take it to the sites of residual myeloma. Understanding this effect and how these two treatments might be combined is actually one of the major issues we are interested in moving forward.

Detail

RESEARCH OBJECTIVES

Dr Bartee’s work focuses on the treatment of multiple myeloma using the myxoma virus – an oncolytic virus.

FUNDING

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BIO

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