Ruxolitinib – successful graft-versus-host disease treatment

Graft-versus-host disease is a serious complication in leukaemia patients who have been given a blood stem cell transplant from a genetically different person. Prof. Dr. Nikolas von Bubnoff and Prof. Dr. Robert Zeiser from the Department of Haematology, Oncology and Stem Cell Transplantation at Freiburg University Medical Centre initiated a Germany-wide study to show that an active substance called ruxolitinib has a promising therapeutic effect. The researchers from the DKFZ were awarded the 2016 Richtzenhain Prize worth 10,000 euros for their achievement.

Haematopoietic cell transplantation is often the only cure for leukaemia patients. Patients given an allogeneic haematopoietic cell transplant have a 30 to 60% risk of developing graft-versus-host disease (GvHD). This is a dangerous immune reaction in which the T cells of the donor not only recognise leukaemia cells but also the healthy tissue of the blood-cell transplant patient as foreign and attack them. The disease manifests itself as tissue damage in the intestine, skin and liver. The patients develop jaundice, an inflamed skin and suffer from diarrhoea. In 20 per cent of all stem cell recipients, GvHD leads to death due to infection or organ damage. The disease is treated using immunosuppressive drugs such as cortisone.

"About half of the GvHD patients have steroid refractory GvHD, which means that they do not respond to cortisone therapy," says Prof. Dr. Nikolas von Bubnoff from the Department of Haematology, Oncology and Stem Cell Transplantation at the Freiburg University Medical Centre. "When the immune system begins to zero in on a certain structure, it is very effective and cannot easily be countered with drugs." No standard therapy will help, and therapeutic options are therefore very limited," says von Bubnoff.

Janus kinases are involved in inflammatory diseases

The tissue damage is caused by inflammatory reactions that are mediated by chemical messenger substances, so-called cytokines. When they are activated, T cells expand by multiplying, thus amplifying the mechanism. It is known that inflammatory immune responses are often driven by a certain group of enzymes that are associated with cytokine receptors. The receptor depends on these Janus kinases, i.e. cytoplasmic tyrosine kinases, to be able to transmit signals. The Janus kinases JAK1 and JAK2 are coupled to the receptor and supply the reaction energy: the binding of cytokines (such as interleukins or interferons) to their receptor leads to activation and mutual phosphorylation of the kinases. This triggers the JAK-STAT signalling pathway. STAT is a transcription factor (signal transducer and activator of transcription) that induces the transcription of proinflammatory cytokines and chemokines in the cell nucleus. This leads to an
increase in T cell production and recruitment. Inflammation takes its course and fuels itself. “It is known that patients with GvHD have an extremely high concentration of inflammatory agents,” explains von Bubnoff.

Can ruxolitinib help?

Eight years ago, Bubnoff had an a Eureka moment at a haematological conference: someone presented data that showed that a certain drug can inhibit inflammatory cytokines in people suffering from myelofibrosis, another malignant disease of the blood-forming bone marrow. “When I saw the poster I immediately realised that the cytokine pattern was exactly the same as in GvHD,” says von Bubnoff. Ruxolitinib is a tyrosine kinase inhibitor that was approved in 2012 for the treatment of myelofibrosis. It interferes with a neuralgic point, i.e. at the point where the inflammatory effector cascade is set in motion. Ruxolitinib blocks the activity of the Janus kinases by competitively inhibiting their ATP binding domains. Without ATP, the kinases can no longer mutually phosphorylate each other. This suppresses the production of inflammatory cytokines, which in turn prevents the proliferation of T cells.

The two haemato-oncologists saw this as a great opportunity and initiated a clinical trial on the efficacy of ruxolitinib in acute GvHD. The researchers have already successfully demonstrated in cell and animal models as well as in retrospective analyses with pilot patients that the cytokines were actually inhibited by the kinase inhibitors. The animals and patients showed fewer GvHD symptoms, survived longer and large numbers were even cured. “We have seen that ruxolitinib not only has a short-term effect, but might even be a disease-modifying therapy that can be used to cure GvHD,” says von Bubnoff.

Richtzenhain prize for translational cancer research

Zeiser and Bubnoff were awarded the 2016 Richtzenhain Prize for their discoveries. The prize comes with a purse of 10,000 euros and is awarded every year by the German Cancer Research Center to researchers who translate ground-breaking results from cancer research into everyday clinical practice. “The prize is awarded in recognition of the successful transfer of research results into a concrete clinical application,” says von Bubnoff. “My colleague, Prof. Zeiser, and I were very pleased to have been awarded the prize.”

Zeiser and Bubnoff launched a multi-centre prospective trial in 15 transplant centres in Germany in April 2017. The trial will run for five years and involve 148 patients. The goal is to obtain marketing authorisation for ruxolitinib for the treatment of graft-versus-host disease. The independent, randomised trial is sponsored by German Cancer Aid and the Federal Joint Committee. Ruxolitinib will be used for patients who do not respond to standard therapy. The trial will determine the serum levels of proinflammatory cytokines and the patients’ response to ruxolitinib by monitoring the clinical GvHD grade.

Ruxolitinib therapy is well tolerated

In addition to the drug response rate, von Bubnoff and Zeiser will also focus on the cost efficiency of the ruxolitinib treatment. They will, for example, assess whether ruxolitinib treatment can replace expensive hospital stays. From day 56 onwards, the ruxolitinib concentration will be tapered off over several weeks in order to prevent excessive cytokine activation (rebound) from occurring after patients stop taking the drug. Although the therapy is well tolerated by patients, it nevertheless further reduces the blood cell count as the inhibited cytokines also play an important role in haematopoiesis. However, red blood cells and blood platelets can easily be replaced. Furthermore, around a third of patients might become infected with CMV (cytomegalovirus) after treatment, which is a side effect resulting from suppression of the patient’s immune system. Some patients will therefore have to undergo antiviral medical treatment.
Von Bubnoff's scientific focus is on molecular therapies in haemato-oncology and the study of biomarkers for the therapeutic monitoring of tumour diseases. Zeiser is specifically interested in transplantation immunology and looking for mechanisms that favour the pathogenesis of GvHD after an allogeneic transplant. As an immuno-oncologist he is very interested in immune system mechanisms that might help to fight even solid tumours. Freiburg University Medical Centre is in the fortunate position of having a molecular tumour board which develops individualised therapies for patients who are in particular difficulty.

"As far as therapy with ruxolitinib is concerned, the next step could be to administer ruxolitinib as the first-choice therapy and drop cortisone altogether," says von Bubnoff. "Perhaps this turns out to be better than what is currently used as standard therapy. Maybe it could eventually also be used preemptively."