



Success stories in leukaemia research

“It started with me feeling ever more listless and my appetite getting ever worse. When my parents found that I was also very pale, we visited (...) a doctor to get my blood checked,” writes twelve-year-old Vera on the website of Initiative krebskranker Kinder München e. V.¹ Tests revealed that Vera had leukaemia. She made up her mind that she would trust her doctors and remain strong. In the meantime, she has seven and a half months of therapy behind her, and only has two more injections to go. “I’m feeling great”, writes Vera. She’s done it.

In western industrialized countries, leukaemia is the most common cancer among children. In Switzerland, around 60 children are newly diagnosed every year, and in Germany about 600.^{2, 3} Leukaemia is a tumour disease of the immune system. In the overwhelming majority of cases, the children affected have acute lymphatic leukaemia (ALL). In ALL, the precursor cells of the lymphocytes (immune cells) remain “stuck” in their immature state during development for a variety of reasons. Frequently it is the so-called pre-B cells that are affected (B-ALL), while more uncommonly it is the (pre)-T cells.

The reason why this aberrant maturation process in acute leukaemia rapidly leads to a dramatic clinical picture lies in two important characteristics of (precursor) immune cells: they can spread throughout the circulation and “flood” all the organs without any problem and they have the ability to replicate extremely fast; hundreds of billions of new cells (10 to the power of 11!) are formed in the haematopoietic (blood-forming) tissue of the bone marrow each day.⁴

Uncontrolled proliferation of the leukaemia cells disrupts the normal formation of blood cells, with the result that fewer red blood cells and also fewer platelets can be produced. The body’s oxygen supply and blood coagulation suffer as a result of this shortage, so the child becomes pale and listless, and bleeding occurs. The tumour cells spread from the

bone marrow to the spleen, liver, lymph nodes and also the central nervous system. Not only the bones become painful, but also the organs in the abdominal space and the lymph nodes, which swell under the onrush of leukaemia cells.

Because the treatment options have steadily improved in recent years, most children today survive leukaemia and are cured. In the case of B-ALL, for example, the survival rate has increased from 10 % in the 1970s to 90 % today (40 % of adults affected survive this disease). This huge advance in treatment is due not only to stem-cell transplantation, write Camille Malouf and Katrin Ottersbach from the Centre for Regenerative Medicine at the University of Edinburgh.⁵ A further essential element that made the development of effective therapies possible was the success of research into the molecular processes that lead to leukaemia.

“This progress would not have been conceivable without animal research”, says Jean-Pierre Bourquin from the Centre for Oncology at the University Children’s Hospital Zurich and the Comprehensive Cancer Centre Zurich.⁶ Research on child cancers is especially difficult, because it is hardly possible to get at the cells and there is too little tumour material available for studies, says Bourquin. Only thanks to studies in mice, it is possible to gain an ever better understanding, for example, of how the haematopoietic system works, what changes in the development of cancer and which genes are involved in the

various leukaemia variants, explains the paediatrician and oncologist.

When are studies in mice in combination with cell culture indispensable? Three examples from current research.

1. New treatment option for patients with a rare treatment-resistant variant of ALL

Most cases of leukaemia in children can be treated successfully. But treatment-resistant, recurrent variants of the disease continue to pose problems for physicians. In cell culture tests two years ago, an international research group headed by Jean-Pierre Bourquin tested 60 different medicines for their effect on 68 (mostly resistant) leukaemia cell samples obtained from different patients.⁷ The cells of some patients responded especially well to the medication Venetoclax, which was recently approved for the treatment of chronic leukaemia in adults. (Venetoclax promotes the death of tumour cells by inhibiting the molecule Bcl-2. This molecule inhibits natural cell death, or apoptosis. A particularly large number of Bcl-2 molecules are generally found in cancer cells.)

To establish whether the combination of Venetoclax with a classical chemotherapeutic agent can be suc-

cessful in treating resistant leukaemia, the scientists used a so-called xenograft model. In this model, human leukaemia cells are implanted in mice whose own immune system has been almost entirely switched off by means of a genetic engineering trick. "Consequently, a disease develops in the animals that is very similar to leukaemia in humans," says Bourquin.

This approach, which has been available for about ten years, enabled researchers to test the tumour material – which is otherwise difficult to obtain and then only in very small quantities – in a "natural" environment and to address important questions that were impossible to answer before, says Bourquin. "We go from the patient to the mouse and back again to the patient," says the research scientist. These are important steps, he adds, to test new approaches. "Because the mouse model enabled us to obtain good data on the efficacy of a combination therapy using Venetoclax and classical chemotherapy, we could venture the leap into its use in humans," the Zurich researcher explains. An initial trial in a young US American patient proved highly promising.⁸

2. Improved therapy and the bone marrow

The uncontrolled proliferation of leukaemia cells



has an impact on the bone marrow. The bones become painful, the bone marrow tissue changes and there is a gradual loss of bone (bone resorption). Scientists from the University of Western Australia in Perth have taken a close look at the bone marrow changes in children with leukaemia.⁹ Biopsies show that tumour cells displace other cells, such as fat cells and bone-forming cells (or osteoblasts), and activate bone-resorbing cells (or osteoclasts).

As in the affected children, researchers also found marked bone loss in mice with leukaemia. This was due amongst other things, say the Australian scientists, to the fact that the bone-resorbing cells, the osteoclasts, became more active under the influence of the tumour cells. In the experiment with mice, the additional administration of a medicine (zoledronic acid) protected against bone loss, reduced the symptoms and prolonged the survival of the animals. The study, say the researchers, provided valuable evidence to suggest that treatment outcomes could be improved and the leukaemia-induced bone loss in affected children can be diminished by medication.

3. Prevention

Leukaemia in children is rare, but the incidence is steadily rising - in the last few decades, the rate of new diagnoses has increased by 1 percent each year. Since this increase is only seen among children who live in countries with a high socio-economic status, it is likely that environmental factors and/or lifestyles are implicated in the development of the cancer.

Ionizing radiation (x-rays, radioactive radiation) increases the risk for leukaemia, as might pesticides, tobacco smoke, exhaust fumes or household chemicals as well.¹⁰ According to current research, the development of leukaemia is dependent on two harmful events occurring at the level of the molecules and genes in the affected cells. The first event usually occurs already during pregnancy, when there is a change in the number of chromosomes or changes in the location of certain chromosome sections. These changes occur in more than 1 % of the population, but they do not have any effect unless a second "event" occurs as well (possibly relating to the time and severity of certain infections).

Researchers from several British universities have now established, thanks to studies in cell culture and mice, that various environmental chemicals have a hitherto unknown effect on the placenta.¹¹ Even if an environmental toxin cannot cross the placenta and enter the baby's bloodstream, according to the latest research results, it does initiate harmful processes. Under the influence of the toxin, the cells of the placenta become stressed and release factors that can cause damage to the DNA in the umbilical cord blood and the stem cells in the haematopoietic bone marrow.

An ever better understanding of the processes through which environmental factors contribute to the development of cancer is at least as important as the development of new therapeutic agents. "Studies in mice, of course, always have the character of a model," says Jean-Pierre Bourquin. But, he adds, they do enable us to understand the links within a complex organism and are thus much closer to real events than laboratory studies in cultured cells - especially since it is rarely possible to keep leukaemia cells stable in culture after they are taken directly from the patient.

Quellen:

- ¹ https://www.krebs-bei-kindern.de/info/berichte/erf_kid6.php
- ² [https://www.zora.uzh.ch/id/eprint/81607/1/04-akute_leukaemien.neu_\(1\).pdf](https://www.zora.uzh.ch/id/eprint/81607/1/04-akute_leukaemien.neu_(1).pdf)
- ³ <https://www.kompetenznetz-leukaemie.de/content/aerzte/epidemiologie/>
- ⁴ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5161115/>
- ⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5765206/>
- ⁶ <http://www.cancercenter.usz.ch/ueber-das-zentrum/organzentren/seiten/onkologisches%20zentrum-universitaets-kinderspital-zuerich.aspx>
- ⁷ <http://www.bloodjournal.org/content/129/11/e26/tab-figures-only?sso-checked=true>
- ⁸ <https://www.futuremedicine.com/doi/full/10.2217/fon-2018-0121>
- ⁹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6224400/>
- ¹⁰ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3839796/>
- ¹¹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6416312/>

It would be ideal if we could understand the complex mechanisms in living organisms without animal experiments. Unfortunately this is not possible yet. The dilemma will remain for quite some time: basic research without animal experiments would mean abandoning medical progress. "Mice times" reports on success stories in medical research that were only possible due to animal experiments.

IMPRESSUM

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