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Case study: Wolfgang Kintzel

Multi-cytokine profiles inform treatment decisions

Proteomics is an indispensable tool for elucidating disease etiology. Advancing our understanding of the molecular background of a disease will enable the development of more effective drugs and precise, reliable diagnostics. Today, researchers worldwide are looking at entire protein networks in cells and organisms to understand the mechanisms of life and translate this knowledge into powerful clinical approaches in medical science.

In this article we describe how the use of a tool called multiplex protein profiling, which involves the simultaneous measurement of multiple cytokines, enabled the assessment of adult patients for the risk of graft-versus-host disease (GvHD) following umbilical cord blood transplantations.

Our study was conducted in 2017 by Vassiliki Boussiotis MD PhD and her team from the Beth Israel Deaconess Medical Center and the Harvard Cancer Center in Boston, US with the support of our Cologne, Germany-based biotechnology company AYOXXA Biosystems GmbH. In the study, the clinical research team simultaneously measured multiple cytokines to assess the risk for GvHD and discovered unique correlation patterns among the adult patients undergoing immune reconstitution.

History

The history of umbilical cord blood transplantation goes back to France in 1988 where the procedure was used to treat a child with Fanconi anaemia, a rare inherited blood disorder. Since that time, the procedure has become one of the most common sources of haematopoietic stem cells for patients with haematologic diseases who can be cured by an allogeneic transplantation. Umbilical cord blood transplantations have a number of advantages compared with haematopoietic stem cell transplantation: the stem cells are easy to procure; there is no risk to the donor and the risk of transmitting infections is low. In addition, they can be easily stored and are well tolerated by the patient's immune system, allowing for successful transplantations despite human leukocyte antigen disparity.

Only 30% of patients who require an allograft will have a human leukocyte antigen (HLA)-matched sibling donor. For the majority of patients, a suitably matched, unrelated volunteer donor cannot be found in the required time. Umbilical cord blood transplantations have the potential to significantly increase access to transplantation and thereby extend the indications for stem cell transplantation. However delayed and insufficient immune reconstitution leading to infection and delayed acute GvHD are the main causes of non-relapse mortality and worse survival.

The goal of our study was to use a novel approach to assess the risk of acute GvHD and an impaired immune reconstitution of adult patients who had received umbilical cord blood transplantations. Potentially, such an approach could guide therapeutic decisions and help prevent life-threatening conditions that might arise from these complications.

Because reconstitution of haematopoietic lineages is delayed in these patients, the clinical research team focused on cytokines which can be measured in a patient's plasma at any time before or after the transplantations. Testing of individual cytokine levels by standard methods such as the enzyme-linked immunosorbent assay (ELISA) requires significant sample volumes and multiple separate assessments. In addition, it is costly and time consuming.

Instead, the study used our company's multiplex protein detection system which comprises a panel of highly specific antibody pairs against 11 cytokines. These included interleukin 8 (IL-8) and tumour necrosis factor-alpha (TNF-alpha). The 11 cytokines are involved in cell-mediated immunity and humoral response as well as changes caused by inflammation in different pathogenic conditions including allergic and autoimmune disorders, immune response to extra- and intracellular pathogens and extracellular parasites.

The study enrolled a homogenous cohort of 27 patients who were treated with the same conditioning and had the same GvHD prophylaxis. Patients were monitored over 24 months by taking periodic blood samples. Multiple cytokines were measured simultaneously and categorised into four different groups based on their kinetics following transplantation. Cytokine levels and immune cell fractions were assessed and correlated at baseline and at six points in time showing a distinctive biomarker signature at the second month post transplantation.

The study revealed very informative cytokine profiles. For example, IL-8, an important mediator of the immune reaction, was the cytokine with the smallest variation during the post-transplant period. IL-8 levels were negatively correlated with antigen-presenting cell counts, namely CD14+ and CD20+ at two months and 100 days post-transplantation negatively correlated with CD4+ immune cells such as T helper cells, monocytes or macrophages six months after transplantation. IL-8 was positively correlated with the immune response, down regulating regulatory T cells (CD4+ and CD25+) and levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), stimulating stem cells to produce granulocytes and monocytes, and was positively associated with cytotoxic T cells (CD8+) at two months after transplantation. Further analyses of correlations between multi-cytokine profiles and clinical outcomes are ongoing.

The results from this initial pilot study suggest that the multi-cytokine profile analysis might serve as a biomarker to guide patient management, such as doing a work-up for infectious complication profiles and treatment options in the early intervention in acute GvHD. This would significantly increase the safety and success rates of umbilical cord blood transplantations.

This article was prepared by Wolfgang Kintzel, Co-Chief Executive Officer, AYOXXA Biosystems GmbH, in Cologne, Germany.