Tailored doses of cytostatic improve survival rate

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Researchers at Karolinska Institutet in Sweden, and colleagues at University Children's Hospital Zürich in Switzerland have managed to improve cytostatic therapy for children with the chronic immune deficiency disorder granulomatous disease prior to stem cell transplantation. By tailoring doses of the cytostatics administered before the transplantation, the researchers achieved a higher rate of survival with minimal adverse reactions. Now more patient groups are to undergo the same therapeutic strategy.

The results, which are presented in the scientific journal *The Lancet*, are based on a clinical study conducted at 16 hospitals around the world. Chronic granulomatous disease (CGD) is a rare immune deficiency in children that causes recurrent, often difficult-to-treat bacterial and fungal infections and non-bacterial inflammations of the inner organs, which sometimes develop into tumour-like nodules of inflammatory tissue known as granuloma. By monitoring patients with this disease, the researchers conducting the study developed a protocol for optimising preparatory treatment with cytostatics (cancer drugs) prior to stem cell transplantation. Careful sampling allowed the doses to be adjusted and optimised for each patient, a procedure that resulted in much better survival rates and minimal adverse reactions.

"We can now present a survival rate of 93 per cent, and that with available cytostatics rather than a new drug," says research team member Moustapha Hassan, Professor of transplantation research at Karolinska Institutet's Department of Laboratory Medicine. "This is a terrific result! Particularly so given that it s babies that we can now help."

Stem cell transplantation is the only treatment method available today for CGD, and is usually preceded by a course of cytostatic drugs to help the body accept the transplantation. However, one problem is that excessive doses of cytostatics can harm the recipient's organs, leading to complications such as central nervous system damage and infertility, while insufficient doses can cause the patient's body to reject the transplanted stem cells.

"Babies are extremely sensitive to cytostatics, which makes it especially important to find the right dose for each individual patient," says Professor Hassan. "This we ve managed to do by monitoring the concentration of cytostatics in their blood and adjusting the dose accordingly to obtain optimal levels for maximal effect and minimal toxicity."

The study involved pre-treating the patients with high doses of the cytostatic fludarabine combined with the immunosuppressive drug anti-T-lymphocyte globulin; they were also given lower doses of a cytostatic called busulfan, levels of which were regularly measured in the patients' blood, allowing the dosages to be adjusted to obtain the desired amount. Because the metabolism of and variations in exposure to busulfan are greater in children than in adults, the researchers consider it imperative to monitor blood levels of the drug.

"Our aim is for tailored treatments to one day become standard practice, which will result in higher survival rates and improved quality of life; our results are so good that we have now begun a similar dose study using the same 'old' cytostatics on patients with leukaemia," says Professor Hassan, who is also especially appreciative of the years of support given to this research by the Swedish Cancer Society and the Swedish Childhood Cancer Foundation.

He hopes that the technique can eventually be used in all drug-based therapies to optimise efficacy for individual patients.

More information: 'Reduced-intensity conditioning and HLA-matched haematopoietic

stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study', Tayfun Güngör, Pierre Teira, Mary Slatter, Georg Stussi, Polina Stepensky, Despina Moshous, Clementien Vermont, Imran Ahmad, Peter J Shaw, José Marcos Telles da Cunha, Paul G Schlegel, Rachel Hough, Anders Fasth, Karim Kentouche, Bernd Gruhn, Juliana F Fernandes, Silvy Lachance, Robbert Bredius, Igor B Resnick, Bernd H Belohradsky, Andrew Gennery, Alain Fischer, H Bobby Gaspar, Urs Schanz, Reinhard Seger, Katharina Rentsch, Paul Veys, Elie Haddad, Michael H Albert and Moustapha Hassan, *The Lancet*, Early Online Publication, 23 October 2013, DOI: 10.1016/S0140-6736(13)62069

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