Tailored pre-transplant therapy boosts survival rate in rare immune deficiency

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Chronic Granulomatous Disease is a rare immune deficiency that seriously compromises organ function and is life-threatening, with 20-30 per cent of patients dying within the first two decades of life. Cell transplantation, the only cure available to date, requires chemotherapy prior to transplantation in order to avoid transplant rejection, although there is a risk of complications such as central nervous system damage, organ failure, and infertility. Researchers from 16 university hospitals and 10 countries, including Switzerland, Sweden, and Canada have demonstrated in a clinical study published in *The Lancet* that tailored doses of the pre-transplant drug therapy boosts survival rates to over 90 per cent. This success rate is particularly impressive since most patients were transplanted with donors that are not in the same family as the patient, a situation in which the survival was below 60% with other protocols, making many centers being reluctant even in considering the transplantation.

Very young children, infants, as well as adolescents and young adults suffering from intractable infections and inflammation benefited from this innovative approach. Because variations in the exposure to busulfan, an agent used in the conventional cytostatics-based pre-transplant therapy, and its related impact on metabolism are greater in children than in adults, the researchers considered it imperative to monitor blood levels of the drug especially in children and adolescents. "Our 14 children who were administered this treatment all survived. This outcome goes far beyond our expectations. It has so to speak "emptied" our region from children with the disease", said Montreal-based co-

author Elie Haddad, clinician and scientist, head of the Immunology Division at the mother-child university hospital center CHU Sainte-Justine and a professor in the Department of Pediatrics at Université de Montréal. "Contributing our cohort of children and adolescents into this multicenter clinical trial clearly benefited our patients," said Pierre Teira, co-author, hemato-oncologist at the Blood and Marrow Transplantation Division of the CHU Sainte-Justine and associate Professor in the Department of Pediatrics at Université de Montréal.

"By tailoring doses of busulfan and carefully sampling patients, we achieved a survival rate of 93 per cent with minimal adverse reaction, independent of the age of the patient, even in those with poor prognosis or highly at risk of graft failure and mortality," said lead author and principal investigator Tayfun Güngör, Assistant Professor of Pediatric Stem Cell Transplantation at the University Children's Hospital Zürich. "Two adult patients have fathered children after successful transplantation, a fact that makes me hope that fertility may have been preserved in a lot of children and adults treated with this approach", he continued. Until now, patients would be administered cytostatic drugs to help their body accept the cell transplantation. However, excessive doses of these drugs can harm the recipient's organs, while insufficient doses can cause the patient's body to reject the transplanted stem cells.

Chronic Granulomatous Disease causes recurrent, often difficult-to-treat bacterial and fungal infections and non-bacterial inflammations of the inner organs, which may lead to organ dysfunction (such as bladder and kidney problems) and endanger life. Up to one-third of children affected die before the age of 20, and those entering adulthood are often handicapped with compromised organ functions and low quality of life.

The investigators' aim is for tailored treatments to become standard practice in other primary immunodeficiencies and non-malignant diseases. Indeed, Prs. Drs. Güngör, Haddad, and Teira are already using

this regimen with success in other primary immunodeficiencies and non-malignant diseases.

More information: "Reduced-intensity conditioning and HLA-matched haematopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study," *The Lancet*, October 23, 2013.

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