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EDITORIAL

Treatment of umbilical cord blood units with interleukin-15 improves hematopoietic stem cell engraftment[☆]



El tratamiento de unidades de cordón umbilical con interleucina 15 mejora el injerto de células madre hematopoyéticas

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Umbilical cord blood is increasingly used as a source of hematopoietic stem cells for transplantation due to less stringent Human Leukocyte Antigen (HLA) matching requirement, rapid availability of the graft and lower incidence and severity of graft versus host disease observed post umbilical cord blood transplantation.¹

Umbilical cord blood transplantation has many advantages but it also has some disadvantages such as delayed immune reconstitution and engraftment, graft failure, higher incidence of infection, limited cell number and no possibility of donor lymphocyte infusion (DLI). Many studies are focusing on overcoming these issues by increasing the cell dose of umbilical cord blood units for adult patients by performing double umbilical cord blood transplantation or ex vivo expansion of umbilical cord blood hematopoietic stem cells, intra-bone infusion of umbilical cord blood, expanding specific cell population such as natural killer (NK) cells or regulatory T cells, using cytokines to enhance

NK cell cytotoxicity or growth factors in order to improve thymopoiesis.¹

NK cells are innate immune lymphocytes that reconstitute after umbilical cord blood transplantation and key effectors of the graft versus leukaemia effect.¹ Interleukin (IL)-15 is a cytokine that induces NK cell maturation, proliferation, survival and differentiation.² The infusion of NK cells together with IL-15 has been tested in phase I clinical trials for patients with acute myeloid leukaemia or solid tumours showing that therapy to be feasible and safe while reducing relapse rate, inducing expansion of donor NK cells, and increasing engraftment.^{3,4} However, even if these results are promising, further studies need to be done to consolidate a therapy. For example, NK cells were infused between days 7 and 30 after haplo hematopoietic stem cells transplantation leading to an improved anti-tumour effect in vitro with no toxicity, but when NK cells should be infused for this therapy to be optimal is still unclear.

We have recently shown that umbilical cord blood NK cells are better activated by IL-15 than other cytokines such as IL-2, IL-12 or IL-18.² In addition, we found that IL-15 activated NK cells could facilitate engraftment of umbilical cord blood hematopoietic stem cells while also increasing their homing to the bone marrow and clonogenicity.⁵ Our results suggest that the co-infusion of IL-15 activated autologous umbilical cord blood NK cells together with the graft could double the levels of engraftment after umbilical cord

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blood transplantation. Therefore, we are currently testing whether the treatment of the umbilical cord blood graft with IL-15 could improve hematopoietic stem cells homing to the bone marrow and increase their clonogenicity in a similar manner as this therapy could lead to improve neutrophil and platelet engraftment in umbilical cord blood transplantation patients and long-term be an alternative to the use of double umbilical cord blood transplantation.

We are evaluating the possibilities to either treat a whole umbilical cord blood unit with IL-15 prior infusion to the patient as well as developing a NK cell therapy to improve engraftment by optimising the selection of NK cells from 20% of a umbilical cord blood unit, so the selected, IL-15 activated NK cells could be added to the rest of the graft prior infusion. In this context, we are planning to test such an approach in a first instance in the context of double umbilical cord blood transplantation infusing one non-manipulated unit and one treated with IL-15 or IL-15 activated NK cells to evaluate the safety, feasibility and clinical activity of this therapy as a way to improve engraftment.

To conclude, the aim of our study is to combine NK cells and IL-15 therapies to improve the outcome of umbilical cord blood transplantation by stimulating umbilical cord blood units with IL-15, with the aim to enhance clonogenicity capacity, homing and engraftment of umbilical cord blood hematopoietic stem cells and therefore improve transplantation outcome due to NK cell activation.

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References

1. Danby R, Rocha V. Improving engraftment and immune reconstitution in umbilical cord blood transplantation. *Front Immunol.* 2014;5:68.
2. Alnabhan R, Madrigal A, Saudemont A. Differential activation of cord blood and peripheral blood natural killer cells by cytokines. *Cytotherapy.* 2015;17:73–8.
3. Pérez-Martínez A, Fernández L, Valentín J, Martínez-Romera I, -Corral MD, Ramírez M, et al. A phase I/II trial of interleukin-15-stimulated natural killer cell infusion after haplo-identical stem cell transplantation for pediatric refractory solid tumors. *Cytotherapy.* 2015;17:1594–603.
4. Rubnitz JE, Inaba H, Ribeiro RC, Pounds S, Rooney B, Bell T, et al. NKAML: a pilot study to determine the safety and feasibility of haploidentical natural killer cell transplantation in childhood acute myeloid leukemia. *J Clin Oncol.* 2010;28:955–9.
5. Escobedo-Cousin M, Jackson N, Laza-Briviesca R, Ariza-McNaughton L, Luevano M, Derniame S, et al. Natural killer cells improve hematopoietic stem cell engraftment by increasing stem cell clonogenicity in vitro and in a humanized mouse model. *PLoS ONE.* 2015;10(10):e0138623.