Immunotherapy with natural killer cells: a possible approach for the treatment of Acute Myeloid Leukemia also in Brazil

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SUMMARY

The allogeneic hematopoietic stem cell transplantation (HSCT) can cure intermediate and high-risk acute myeloid leukemia. Even with the development of strategies to reduce HSCT toxicity, this is still a complex treatment with high morbidity and mortality. Knowledge of the graft versus leukemia effect of HSCT has prepared the way for the development of Adoptive Immunotherapy or *in vitro* expansion of activated lymphocytes without alloreactivity, with subsequent intravenous infusion. The infusion of genetically modified T lymphocytes and haploidentical natural killer cells has been tested as an alternative to HSCT with very interesting results worldwide and in Brazil, as we not only have the technology of *in vitro* expansion of clinical grade lymphocytes available, but also do it according to the Good Manufacturing Practices that have been determined internationally.

Keywords: NK cells, graft versus leukemia effect, adoptive immunotherapy, acute myeloid leukemia.

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The Hematopoietic Stem Cell Transplantation (HSCT) is currently the curative option for intermediate and high-risk acute myeloid leukemia (AML); procedure toxicity and complexity can, however, result in a series of harmful consequences for the body – even when cured of the malignancy. Since the beginning of the 1990s, it has been known that the curative action of HSCT depends on the effect of graft immune cells on residual malignant disease - the graft-versus-leukemia effect - consolidating the knowledge of the immune system role in eradicating malignancy[1].

Immunotherapy based on the use of activated immune cells, also known as Adoptive Immunotherapy (AI), aims to use the patient's own immune cells or those of a selected donor, in order to eradicate the malignant disease without the risk of graft-versus-host-disease (GVHD) development observed in the HSCT scenario. The results of AI, tested initially and for many years in the treatment of solid cancers, particularly melanoma, have become consistent after Rosenberg[2] demonstrated that it is essential to eliminate or attenuate the activity of the patient's immune cells prior to the lymphocyte infusion, as to allow the *ex-vivo* activated lymphocytes, when infused, to find an environment rich in growth factors and thus proliferate and perform their antitumor action markedly and continuously.

The recent development of T-lymphocytes modified by inserting Chimeric Antigen Receptors (CAR) into them and their infusion after the patient's immune system ablation demonstrates the principle that AI is a promising treatment[3]. However, the infusion of CAR lymphocytes, with significant antitumor activity, it followed by tumor lysis syndrome that results in a cytokine storm, of which the patient, if not adequately treated with specific immunological blockers, may die. Fortunately, these are preliminary results obtained in the treatment of patients with significant tumor mass. Perhaps the use of immune effectors in a residual tumor disease scenario might minimize these effects and thus, phase II studies including patients in complete remission of the disease are needed to test this hypothesis.

In the treatment of AML, particularly when using the haploidentical HSCT, the role of natural killer (NK) cells in eradicating the disease dissociated from GVHD was demonstrated[4]. Therefore, NK cells seem to be natural candidates for AI in the treatment of this disease and their infusion, without HSCT, in patients with AML, has shown to be effective[5].

The great challenge has been, however, to achieve the *in vitro* expansion of a population of purified NK cells, with no contamination by T lymphocytes – a very difficult

task, because NK cells are relatively rare in peripheral blood. The development of cells with artificial antigens that received the insertion of adhesion molecules and specific cytokines, when co-cultured with mononuclear cells previously depleted of T lymphocytes, has been shown to be a promising technique to obtain up to 1010 NK cells with purity levels >90%[6].

This technology is established in Brazil, more precisely in the Technology and Cell Therapy Center of Porto Alegre University Hospital. A clinical trial about the safety and feasibility of AI with expanded NK cells for the treatment of recurrent or treatment-refractory AML has already been approved in Brazil and ongoing at MD Anderson Cancer Center (MDACC), in Houston, TX, USA. The first three patients that have already treated in Houston have shown that not only the infusion of these cells is not accompanied by any adverse effects, but also that the answer seems to be slow and gradual, as four months after treatment the disease residual levels remain decreased, demonstrating not only the antitumor action of these cells but also the permanence of these cells or their effect for a prolonged period. The inclusion of the first patient treated in Brazil should take place within a few weeks. In a review recently published by our group[7] it is possible to have a broader and more comprehensive view of the role of NK cells in the treatment of neoplasms.

Resumo

Imunoterapia com células *natural killer*: um caminho possível para o tratamento da Leucemia Mielóide Aguda também no Brasil

O transplante de células-tronco hematopoéticas (TCTH) alogênico é curativo para leucemia mielóide aguda de risco intermediário e alto. Mesmo com o desenvolvimento de estratégias para minorar a toxicidade do TCTH, este ainda é um tratamento complexo com elevada morbi-mortalidade. O conhecimento sobre o efeito enxerto contra leukemia do TCTH pavimentou o caminho para o desenvolvimento da Imunoterapia Adotiva ou expansão *in vitro* de linfócitos ativados, sem alo-reatividade, com posterior infusão endovenosa. A infusão de Linfócitos T geneticamente modificados e de células Natural Killer haploidenticas tem sido testada como alternativa ao TCTH com resultados bastante interessantes no mundo e no Brazil já que não apenas dominamos a tecnologia de expansão *in vitro* de linfócitos em grau clínico, como o fazemos segundo as Boas Práticas de Manufatura determinadas internacionalmente.

Palavras-chave: Células NK, efeito enxerto contra leucemia, imunoterapia adotiva, leukemia mieloide aguda.

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