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# Intra-bone route of donor lymphocyte infusion favors anti-leukemic allo-reactivity not increasing the risk of acute GvHD

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Graft vs. Leukemia effect preventing relapse in patients with hematologic malignancies receiving allogeneic hematopoietic stem cell transplantation (alloHSCT) can be augmented by infusion of donor lymphocytes (DLI) in patients at the risk of relapse. However, this procedure can ignite the graft vs. host disease in about 30% of patients post DLI. The lower rate of leukemia relapse in patients receiving alloHSCT as opposed to patients post autoHSCT prompted us to develop a new approach in DLI delivery to facilitate anti-leukemic allo-reactivity not increasing the risk of GvHD. The aim of our study is to regenerate the immune system originated from transplanted (HSCT) material especially within the lymphocyte compartment exerting cytotoxic potential but not facilitating GvHD. The elaborated and clinically implemented approach consisted of the following steps: (1) Identification of relapse post alloHSCT with the presence of leukemic cells in the marrow or in the bones in extramedullary relapse; (2) Obtaining from the donor of mononuclear cell population containing 61%±2.34 (sem) of CD3+ cells in the lymphocyte gate with the use of cell separator; (3) The cells are divided into portions securing CD3+ cells infusion in a dose of 10E6 kg-1 BW for the first infusion, 10E7 for the second approach and 10E8 for the third infusion, frozen in the liquid nitrogen and stored in our tissue bank and (4) Donor cells are injected directly to the posterior iliac crest in patients with marrow or, to the affected bones in patients with extramedullary relapse. The 17 procedures were performed in 5 patients. To have an access to the marrow cavity or to the bones affected by leukemia, the routine trocar for bone harvesting or the bone injection gun, were employed, respectively. The procedure was safe and well tolerated and no symptoms of GvHD were noted after the procedures. In a patient with extramedullary relapse, the healing of the bone lesions was seen clinically and in the evaluated nuclear resonance images. The positive response lasted 7 months until the fatal marrow relapse emerged. In 4 patients with medullary relapse, the reduction of leukemic cells or stable disease was seen in all patients except one, after 1st and 2nd DLI procedures. The patients were under the observation from 3 to 16 months. The positive response was consolidated either by the second transplant (2 patients) or the maintenance approach with the use of Sorafenib (1 case) or anti-CD20 MoAb (one CLL case). Notably in all marrow evaluations performed along the treatment, there was an excess of CD8+ cells in the marrow as compared to the blood especially seen within CD8+ and CD279+ cells compartment. In conclusion, an accumulation of CD8+ donor lymphocytes harboring CD279+ cells in the marrow cavity of patients relapsing post alloHSCT receiving IB-DLI associates with a positive anti-leukemic response. This observation strongly suggests the presence of T cells cytotoxic response in the marrow infiltrated by leukemia restored by IB-DLI.

## Biography

Andrzej Lange has graduated with a Medical degree with distinction from the Medical School in Wrocław, Poland. Currently, he is a Professor in the Institute and Founder and Head of the Lower Silesia Center of Cellular Transplantation in Wrocław. His international experience started as a Leverhulme Fellow in the Middlesex Hospital Medical School, London. During 8 year period, he used to spend three months yearly as a Visiting Scientist in the Institute of Experimental Medicine and Biology in Borstel, Germany. He has been a Short Term-Visitor and lectured in a number of European and North American scientific institutions. He is author of 239 scientific papers in peer-reviewed journals.

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