Development of an adoptive cell therapy protocol with tumor-infiltrating lymphocytes and intermediate-dose interleukin-2 therapy

Linh T Nguyen1*, Marcus O Butler2, Pei Hua Yen1, Jessica Nie1, Michael Pniak1, Alisha R Elford1, Anthony M Joshua2, David Hogg2, Danny Ghazarian3, Ayman Al-Habeeb3, Alexandra M Easson4, Wey L Leong4, David R McCready4, Michael Reedijk4, Hans A Messner2, Pamela S Ohashi1,5

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Adoptive cell therapy (ACT) with tumor-infiltrating lymphocytes (TILs) has shown promising results in early phase trials. In an approach developed by the Rosenberg group at the Surgery Branch (NCI), patients with metastatic melanoma receive a pre-conditioning regimen of cyclophosphamide and fludarabine-induced lymphodepletion (+/- total body irradiation), followed by infusion of autologous TILs and high-dose interleukin-2 (IL-2) therapy. At our institution, we have established the technology to produce therapeutic-grade TILs. Our preclinical work included adapting protocols from the Surgery Branch to expand TILs from melanoma lesions, setting up a program to obtain blood products from healthy donors to support the in vitro expansion of TILs, and establishing Standard Operating Procedures for production of therapeutic-grade TILs. In order to generate sufficient numbers of cells for infusion, TILs are subjected to a “Rapid Expansion Protocol” (REP) using anti-CD3 antibody (OKT3), feeder cells (irradiated peripheral blood mononuclear cells) and interleukin-2. In our preclinical work, we found that the REP could be performed using concentrations of IL-2 that are lower than those usually used: 300 and 600 IU/ml of IL-2 induced similar fold-expansion and CD4:CD8 ratios as 3000 IU/ml of IL-2. Survival of TILs in vitro after the REP in various concentrations of IL-2 was also assessed. We reasoned that TILs that had been rapidly expanded in a lower concentration of IL-2 would subsequently not require high-dose IL-2 after infusion in order to mediate clinical responses. If this is the case, use of a lower dose of IL-2 therapy for TIL protocols would improve the toxicity profile of ACT and reduce resources needed for inpatient care. In order to explore this hypothesis, we have designed a clinical trial of cyclophosphamide and fludarabine followed by TIL infusion and an intermediate dose of IL-2 therapy (125,000 IU/kg for 2 weeks with 2 days rest in between each week). Institutional and federal regulatory approvals have been obtained for this trial.

Authors’ details
1Campbell Family Institute for Breast Cancer Research, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada.
2Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada.
3Department of Pathology, University Health Network, Toronto, ON, Canada.
4Department of Surgical Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada.
5Department of Immunology, University of Toronto, Toronto, ON, Canada.

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