TK cell therapy

Chiara Bonini

Università Vita-Salute San Raffaele, Ospedale San Raffaele IRCCS, Italy

Cellular immunotherapy, and in particular T-cell therapy, have recently produced impressive clinical results. Expanded tumor specific T cells, genetically engineered T cells are rapidly entering the clinical arena. The most effective and consolidated cell therapy approach is allogeneic haematopoietic stem cell transplantation (HSCT), the only cure for several patients with high-risk haematological malignancies. The potential of allogeneic HSCT is strictly dependent on the donor immune system, particularly on alloreactive T lymphocytes, that promote the beneficial graft-versus-tumour effect (GvT), but may also trigger the detrimental graft-versus-host-disease (GvHD). Gene transfer technologies allow to manipulate donor T cells to enforce GvT and foster immune reconstitution, while avoiding or controlling GvHD. The suicide gene approach is based on the transfer of a suicide gene into donor lymphocytes, for a safe infusion of a wide T cell repertoire, that might be selectively controlled in vivo in case of GvHD. The herpes simplex virus thymidine kinase (TK) is the suicide gene most extensively tested in humans. Its expression in donor lymphocytes confers to the cells (TK-cells) lethal sensitivity to the anti-herpes drug, ganciclovir. Progressive improvements in suicide genes, vector technology and transduction protocols have allowed to overcome the toxicity of GvHD while preserving the antitumor efficacy of allogeneic HSCT. Several phase I-II-III clinical trials documented the safety and the efficacy of the TK-cell approach. The activation of the suicide machinery prooved highly effective in abrogating acute GVHD in all reported trials, resulting in conditional approval by the European Medicines Agency (EMA) of a gene therapy medicinal product consisting of TK-engineered allogeneic T lymphocytes. The experience gained through the preclinical and clinical development of TK-cells have been also instrumental for shaping innovative, genetically engineered cellular products, for cancer immunotherapy. Challenges and opportunities will be discussed.