

Cell Therapy Strategies are also Promising to the Future of Immunotherapy

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Received date: Mar 10, 2014, Accepted date: Apr 22, 2014, Published date: Apr 29, 2014

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Keywords: Immunotherapy; Acute myeloid leukemia; NK cells

Letter to Editor

We read with interest the article Novel Immunotherapy to Eliminate Minimal Residual Disease in AML Patients [1]. Elderly people with AML show resistance or early relapse after standard chemotherapy. It is therefore crucial to look for novel immunologic approaches, because several data support the hypothesis that the loss of interaction between tumor cells and the immunity of the host play a critical role in tumor progression by facilitating tumor escape from immune control [2].

Although we acknowledge that strategies of passive as well as active immunization with vaccines or monoclonal antibodies, such as described by the authors, are currently more commonly employed in the treatment of AML, we believe that cell therapy strategies are also promising to the future of immunotherapy (IT) in AML. In patients with high risk leukemia, monoclonal antibodies such as Gemtuzumab ozogamicin (anti-CD33) in addition to induction chemotherapy for AML can significantly prolong overall survival (OS) and relapse-free-survival (RFS) [3]. Vaccination with disease-associated antigen derived-peptides, such as WT-1 has been shown to cause prolonged remission and decreased relapse [4,5]. However, within the immune system of cancer patients, the efficacy of vaccin-induced, tumor-specific T cells is significantly hampered by the presence of tumor induced-suppression and regulatory tolerogenic factors [6]. Although early trials of peptide vaccination in cancer patients showed promising immunological responses, more recent reports have been predominantly negative [7-9].

Strategies of cell therapy of AML currently employ both natural killer (NK) and T cells. The use of NK cells for IT purposes has been proposed based on the observation that donor NK cells mediate antileukemic activity by enhancing graft versus leukemia (GVL) in AML patients receiving allogeneic T-cell depleted hematopoietic stem cell transplantation (HSCT) [10]. Miller et al demonstrated for the first time that adoptively transferred human NK cells can be expanded in vivo, leading to a clinical improvement with disease responses especially with killer immunoglobulin receptor (KIR) ligand mismatched donors [11,12]. Immunotherapy with NK cells may contribute to the eradication of minimal residual disease (MRD) in AML [10].

Adoptive IT with T-cells requires specificity of the infused cells for leukemia-associated antigens (LAAs), to minimize the risk of unwanted graft versus host reactions. They have been generated in vitro, and may kill leukemic cells in vitro and in vivo, but their clinical use has been hampered by technical difficulties.

Conversely, transferring the gene encoding for a LAA-specific T-cell receptor (TCR) into T cells in vitro has led to leukemia-reactive T cells, but the major limitation of this procedure is that the antigen-specific T-cell lines are restricted to a specific HLA allele, making it necessary to perform costly patient-tailored T-cell generation procedures for each patients [10]. However, the technology of chimeric antigen receptors (CARs) may represent a more easily generalizable approach to T-cell gene therapy, because is HLA-independent and may therefore be used in a broad range of patients. It allows higher specificity and has led to clinical response in clinical trials [13].

We believe that these immunological strategies with relatively low toxicity could improve the outcome especially for poor prognosis AML in the elderly, who rarely can undergo a II line chemotherapy regimen because of their frailty and multiple comorbidities.

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