closed) and Ph-like cases are being identified using a predictor described by our group (Chiaretti et al, BJH, 2018). In adult B-lineage ALL, Ph+ and Ph-like ALL account for 35–60% of cases, depending on age, making them the most prevalent genetic ALL subgroup.

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CAR T-cell in children all

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Chimeric Antigen Receptor (CAR)-T cell therapy is emerging as one of the most powerful and promising therapeutictool for the treatment of malignat diseases. CAR-T cells are T-lymphocytes modified *in vitro* to harbor an artificial molecular construct (CAR) made by an extracellular domain consisting of a single-chain variable fragment (scFv) recognizing a specific tumor antigen joined to a transmembrane domain which is linked to the signaling unit CD3ζ and co-stimulatory units CD28 or 4-1BB of the T-cell receptor, making them capable to recognize and to kill tumor's cell in a HLA-independent manner.CAR T-cell therapy consists in the selection of patient's normal T-cells via leukapheresis, activation, transduction to express CARs using lentiviral or retroviral vectors, expansion of transduced cells and infusion of the final product back to the patient. After the CAR T-cells are infused back into the patient, the engineered cells proliferate, recognize and kill tumor cells bearing the specific antigen the CAR is directed against. Most of the current clinical trials have been with anti-CD19 CAR T-cells directed against the antigen CD19, mainly expressed by Acute Lymphoblastic Leukemia and B-cells Non Hodgkin Lymphomas.

In recent years US Food and Drug Administration (FDA) and European Medicine Agency (EMA) approved CD19 CAR T-cells in patients affected by relapsed and refractory ALL under the age of 25 years and this technology is moving from an experimental approach available for very selected patients treated in a small number of Centers to a standard-of-care therapy available almost worldwide.

The diffusion of this technology requires a re-definition of the role of all the other therapy options currently available including other forms of immuno-therapy as monoclonal antibodies, bi-specific monoclonal antibodies and, upon all, allogeneic hematopoietic stem cell transplantation (alloHSCT).

Until now data are limited, and the above-mentioned question is far from being answered but there are some observations derived from pivotal clinical trials that probably will help us in building future trials aimed to define this topic.

Another open question is represented by the persistence of these cells in the patients that is related to the definition of the need for patients responding to CAR-T cells to proceed to other therapies, especially to alloHSCT, to consolidate disease remission. Moreover CAR-T cells are characterized by some peculiar side effects as the Cytokines Release Syndrome or CNS toxicity that if are not properly detected and treated may lead to very severe consequences with a significant mortality rate.

Finally, some technological, practical and economical considerations need to be defined in order to extend the use of this technology worldwide, in respect to the other currently available therapies.

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SP 13

Update on chimeric antigen receptor – T cells (CAR-T) CD19 therapy: the Sheba experience

Arnon Nagler

Chimeric antigen receptor (CAR) T-cell therapy for hematologic malignancies is a cutting edge therapeutic advancement which is leading the immunotherapy frontier and cancer therapy. CD19-specific CARs are the most commonly used. CD19 is expressed on the surface of most B-cell malignancies and thus can be used as a target for immunotherapies for ALL, and NHL. Phase II trials have showed that anti-CD19 CAR T-cell therapy can induce durable responses in patients with relapse/refractory (R/R) ALL and aggressive B cell NHL. Some of the AMLs with 8:21 translocation expressed CD19, as well. We initiated a single center program in which patients with R/R ALL and NHL were treated with academic produced anti-CD19 CAR T-cells (autologous T-cells expressing anti-CD19 CAR construct with CD28 co-stimulatory domain). Inclusion criteria were age between 1 and 50 years, failure of at least two prior therapeutic protocols, a CD3 count greater than 250/μL blood, absence of clinical signs of graft-versus-host disease and no immunosuppressive treatment. Depending on age, the minimal performance score was 50 on a Lansky scale or on a Karnofsky scale. Patients with prior CD19 directed therapies were eligible for the study. Lympho-depleting conditioning was inducted by fludarabine 25 mg/m^2 for 3 days and cyclophosphamide 900 mg/m^2 for 1 day, followed by infusion of 1–1.5 × 10^6 transduced CAR-T cells per kilogram weight. Primary endpoints of the study were production feasibility, patient safety and best overall response rates, documented 1 to 2 months after infusion. 93 patients with r/r B-cell malignancies. All patients were heavily pretreated. Three enrolled patients (3%) dropped out from the study due to clinical deterioration ($n = 2$) or failure to produce CAR-T cells ($n = 1$; absence of CAR-T cells in the infusion product). One patient was treated twice. Of the treated patients, 37 patients had r/r ALL and 53 patient's r/r NHL, including DLBCL ($n = 36$), Burkitt lymphoma ($n = 3$), PMBCL ($n = 7$), follicular lymphoma ($n = 4$), gray zone lymphoma ($n = 1$), mediastinal lymphoma ($n = 1$) and high-grade lymphoma ($n = 1$). The median age of pts with ALL was 17 ± 14 years and median age of those with NHL was 44 ± 15 years. Both, ALL and NHL patients received an average of three prior lines of therapy. Thirty-two of 90 patients (36%) received a stem cell transplantation(SCT) prior CAR-T therapy, including 17 allogenic or haloidentical SCT in patients with ALL ($n = 15$) and NHL ($n = 2$). Ten of 37 (27%) ALL patients received prior