has proven effective in controlling intravascular hemolysis in vivo, leading to remarkable clinical benefit in a majority of PNH patients.[12,13] Yet, persistent C3 activation occurring during eculizumab treatment may lead to progressive deposition of C3 fragments on affected erythrocytes and subsequent C3-mediated extravascular hemolysis, possibly limiting the hematologic benefit of anti-C5 treatment.[14,15] Thus, upstream inhibition of the complement cascade seems an appropriate strategy to improve the results of current complement-targeted treatment.[16,17]

REFERENCES

1. Hillmen P, Hows JM, Luzzatto L. Two distinct patterns of glycosylphosphatidylinositol (GPI) linked protein deficiency in the red cells of patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 1992;80(3):399–405.
2. Nakakuma H, Nagakura S, Horikawa K, et al. Interleukin-2-dependent T-cell lines established from paroxysmal nocturnal hemoglobinuria patients. Blood. 1994;84(1):309–14.
3. Takeda J, Miyata T, Kawagoe K, et al. Deficiency of the GPI anchor caused by a somatic mutation of the PIG-A gene in paroxysmal nocturnal hemoglobinuria. Cell. 1993;73(4):703–11.
4. de Latour RP, Mary JY, Salanoubat C, et al., French Society of Hematology; French Association of Young Hematologists. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. Blood. 2008;112(8):3099–106.
5. Bessler M, Hiken J. The pathophysiology of disease in patients with paroxysmal nocturnal hemoglobinuria. Hematol Am Soc Hematol Educ Program. 2008:104–10.
6. Fahri Sahin, Melda Comert.

https://doi.org/10.1016/j.htct.2020.09.010

SP 10

Access to cancer medicines and targeted therapies in developing countries

Zeba Aziz

In LMIC national cancer control programs are barely existent. Emphasis is mainly focused on fighting infectious disease, maternal child mortality and now fighting the Covis-19 catastrophe.

Pakistan is a LMIC with allocation of only 2.7% of the GDP to health. We have approximately 173,937 new cancers and a mortality of 118,442. Health expenditures do not correlate with outcomes especially for the marginalized population. Development and implementation of national NCD control programs for screening of common cancers and early detection are either non-existent or sporadic as a result cancers are usually diagnosed late and present challenges to therapy on all fronts especially in the indigent population.

Challenges include poverty, ignorance, lack of access to cancer centers, lack of access to basic cancer therapy and suboptimal treatment. This includes surgery, radiation and cancer therapy including supportive care. Simultaneously there is a dearth of human resource and cancer care providers to diagnose treat and provide supportive care to cancer patients.

Access to new biologics and targeted therapies present a challenge to the already strained health care budget. Current status of cancer care will be discussed in Pakistan.

https://doi.org/10.1016/j.htct.2020.09.011

SP 11

Ph-positive and ph-like all: how can we further improve?

Robin Foà

While in childhood ALL the cure rates can be over 80%, in adults the prognosis still remains unsatisfactory. Important advancements have however occurred in the management of adult patients based on the biology of the disease. Ph+ ALL is an illuminating example of how the understanding of a specific genetic abnormality has led over time to the use of targeted therapies. The results obtained with tyrosine kinase inhibitors (TKI) used upfront in adult Ph+ ALL have changed our approach to this condition in patients of all ages. It is thus mandatory that the abnormality is rapidly investigated at presentation. In the GIMEMA network, the presence or absence of the BCR-ABL fusion is tested centrally within one week from diagnosis of ALL, during the steroid pre-phase. TKIs – alone or in combination with chemotherapy – have markedly improved the rates of response and overall survival of Ph+ ALL. The Italian cooperative group GIMEMA over the years has been using an induction strategy based on the use of a TKI (1st, 2nd and 3rd generation) plus steroids and CNS prophylaxis, with no systemic chemotherapy. This has led to a hematologic CR in 94–100% of patients (with no upper age limit) with virtually no deaths in induction. A proportion of patients can obtain a molecular response. Some elderly patients treated only with TKIs are alive and well after many years from diagnosis. Other groups have used a combination between a TKI and de-intensified chemotherapy, in order to reduce the toxicities (and deaths) associated with conventional chemotherapy plus a TKI. With the advent of TKIs, the induction of Ph+ ALL patients – if identified promptly – is a solved issue. Since patients who achieve a molecular response fare significantly better, a molecular response should be the primary endpoint of treatment. Allogeneic stem cell transplant has always been considered the only curative strategy for Ph+ ALL patients. New strategies are however under active investigation. In the last GIMEMA LAL 2116 front-line trial an induction-consolidation strategy based on the use of dasatinib followed by at least two cycles of the bispecific monoclonal antibody blinatumumab were used. This chemo-free induction-consolidation approach is associated with very high rates of molecular response (Chiaretti et al, ASH 2019). In childhood Ph+ ALL, the protocols so far still use an induction based on a combination of chemotherapy plus a TKI.

Great attention has been raised by the so-called Ph-like ALL, a subgroup associated with an unfavorable prognosis. Evidence has been provided that this is contributed by the persistence of minimal residual disease following conventional chemotherapy. Attempts are being carried out by incorporating TKIs or other inhibitors. The GIMEMA LAL 2317 has used blinatumomab in the front-line Ph- ALL protocol (recently

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.

https://doi.org/10.1016/j.htct.2020.09.012

SP 12

CAR T-cell in children all

Francesco Saglio[1,2]

[1] *Pediatric Onco-Hematology, Stem Cell Transplantation and Cellular Therapy Division, Regina Margherita Children's Hospital, Torino, Italy*
[2] *University of Turin, Turin, Italy*

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.

https://doi.org/10.1016/j.htct.2020.09.013

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