of toxicity and mortality of the procedure especially in patients with comorbidities for age and performance status. But also due to the organ toxicity of the pre-HSCT, conditioning, and transplant-related complications, mainly graft versus host disease (GVHD). On the other hand, allogeneic transplantation mediating the graft versus tumor effect that correlates with GVHD provided the first demonstration of cellular immunotherapy and the ability to tailor the immune system against malignancies. The immune system can recognize and eliminate malignant cells and as such is a powerful tool in fighting cancer.

This was the basis for the development of donor lymphocyte infusions,nonmyeloablative conditioning, and finally the chimeric antigen receptor -T (CAR-T) adoptive immunotherapy that revolutionized anti-cancer therapeutics.

CAR-T cell therapy for hematologic malignancies turns out to be a cutting-edge therapeutic advancement that is leading the immunotherapy frontier and cancer therapy. CD19-specific CARs for lymphatic malignancies including NHL, MM, and ALL revolutionized the field and changed completely treatment paradigms in lymphatic hematological malignancies. Currently, there are 6 commercial CAR-T cell products that are FDA-approved (4 for NHL and ALL and 2 for MM). In general, the toxicities of CAR-T cell therapy are lower than those of HSCT, there are no age limits and CAR-T is effective in patients with chemoresistant, high-risk diseases that failed HSCT. In NHL they are offered already in the second line of therapy and as a result, the number of autologous transplantations is being sharply reduced in NHL and MM. However, there are major issues with the availability and affordability of CAR-T cell therapy, and many patients that are in need cannot receive it, especially in low or medium-income countries. Point-of-care academic CAR T cells may overcome these limitations. We, at Sheba Tel- Hashomer, initiated already in 2016 a point-of-care academic CAR-T cell program in which hundreds of patients with relapsed/refractory ALL, NHL patients (first as the third line, and then patients failing the first line of therapy or relapsed within 12 months), and from 2021 patients with MM are being treated with CD19 and anti-B cell maturation antigen (BCMA) based CAR-T cells, respectively. We also treated a small cohort of patients with AML harboring the 8:21 translocation that expressed CD19 with CAR-T cells. The benefits of point-of-care CAR-T cells are a shorter time, 10-11 days, from a vein (leukapheresis) to the vein (administration) and therefore, almost no need for bridging therapy but mainly lower cost significantly increasing CAR-T cells affordability and accessibility. We will try to discuss these issues in our session.

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Sp03

The revolution in frontline treatment of Multiple Myeloma

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The frontline treatment of multiple myeloma has recently been revolutioned, thanks to the approval of a new backbone, daratumumab, anti-CD38 monoclonal antibody, in both transplant-eligibile and -not eligibile patients.

In transplant-eligible setting, daratumumab has been added, according to CASSIOPEIA trial, to the previous standard-of-care bortezomib-thalidomide-dexamethasone (Dara-VTD), followed by autologous-stem cell transplantation (ASCT), two cycles of consolidation, and oral lenalidomide maintenance until progression.

In transplant-ineligible setting, daratumumab is added, according to MAIA trial, to lenalidomide-dexamethasone (DRD) until progression, or, according to ALCYONE Trial, to bortezomib-melphalan-prednisone (Dara-VMP) x 9 cycles.

Results are incredible in both settings in terms of efficacy and tolerability, with the achievement of very good quality of life for patients, also thanks to the schedules and the subcutaneous administration of daratumumab.

Achieving the deepest response correlates with the best long term result, and that's why, in this scenario, the endpoint becomes not only the achievement of complete response/stringent complete response, but also MRD negativity. That's why the importance of testing accurately the results of the treatment, particularly evaluating MRD during the patient journey, also in real world, is becoming more and more important, not only in order to optimize the use of the drugs, also in maintenance setting, but also to balance correctly efficacy and toxicity.

Ongoing trials are also aiming to evaluate the role of new generation agents, in new quadriplets with potential deepest results but also risk of greater toxicities for which supportive care needs to be improved and standardized.

In next future, ongoing clinical trials aim to evaluate the role of new agents in induction regimens, and also anti-BCMA CAR-T in replacing ASCT, together with the role of bispecific antibodies in maintenance setting, and the idea of MRD-driven approach potentiating or reducing the treatment according to the response.

CAR-T have shown excellent results in heavily pretreated patients, with the limits of tolerability and feasibility, also for costs: the increasing opportunities for academic products could help to improve and optimize the use and also to better evaluate these agents in a less selected population.

Another interesting perspective is to anticipate the treatment, before the onset of symptoms, concentrating efforts on correctly diagnosing and treating high-risk Smoldering myeloma, strongly waiting for results coming from phase 3 trials aiming to compare IMIDs with the combination anti-CD38 antbody, IMIDs and dexamethasone, avoiding ASCT, and permitting to the patients to obtain deep response with a really good tolerability.

In conclusion, in frontline setting, considering the wonderful opportunities that we have in real world, and that are coming in next future, our endpoint, should be to achieve the deepest responses, aiming to MRD negativity, particularly in young and fit patients, balancing with tolerability and quality of life.

This should become the new endpoint of upcoming clinical trials, considering that its achievement could correlates with the best long-term response and could really help us and our patients to the cure of multiple myeloma.

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