HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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ADULT SPEAKER PRESENTATIONS

Sp01

Induction therapy choices and responses in a third world country: A single center study from Pakistan

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A B S T R A C T

Background: Leukaemia accounts for approximately 2.5% of all new cancer incidence and 3.1% of cancer-related mortality with a significant number of the total presenting as Acute Lymphocytic Leukemia. Acute Lymphocytic Leukemia (ALL) poses a healthcare burden in the majority of the countries of the world but is more so a case in resource-limited countries where access to comprehensive healthcare is often limited and scarcely available. This article tries to highlight the challenges in ALL treatments in one such region by presenting the facts regarding treatments employed and patient outcomes seen.
Method: This was a retrospective single-institution study in a tertiary care setup examining Ph neg ALL patient data from Jan 2019 to Dec 2020. It was stratified according to various parameters ranging from presentation to mode of diagnosis as well as treatment strategies and responses achieved after induction including mortality. Conventional chemotherapy regimens for ALL treatment were used with corticosteroids, vincristine, anthracyclines, asparaginase, cytosar, and MTX being the backbone of ALL induction. Cytogenetics were not possible due to resource constraints.
Results: Data showed 85 patients being managed during the mentioned time period. 65 percent were males and 68 percent were between the age 15 to 30 years. Approximately 80 percent had no co-morbid condition including diabetes, hypertension, ischemic heart disease or Hep B/C positivity. Around 60 percent were diagnosed on immunophenotyping by flowcytometry and 62 percent used HyperCVAD as the induction protocol. Patients who achieved CR were 62 percent after single induction and most were assessed after count recovery on (3-4 weeks) or after 6 weeks with the percentages being 32 and 41 respectively. Duration of admission was for 1-3 weeks for almost 70 percent of the patients and those alive at the end of induction were around 90 percent.
Conclusion: In conclusion, the treatment of Acute Lymphocytic Leukemia in resource-limited countries remains a formidable task,sometimes requiring innovative and sustainable approaches. Due to limited resources, a resource stratified rather than risk-stratified treatment approach is often utilized to tailor therapy. This approach ensures that relatively better resourced patients receive more intensive treatment others are spared unnecessary toxicity. While the challenges in resource-limited settings are significant, the treatment strategies and chemotherapy protocols, if modified as per need and implemented effectively, hold promise in improving outcomes for patients with Ph negative Acute Lymphocytic Leukemia in regions which have limited resources at their disposal.

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Sp02

Bone marrow transplantation versus chimeric antigen receptor T cells (CAR-T) therapy for hematological malignancies

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Hematopoietic stem cell transplantation (HSCT) is an effective curative therapy for a long list of hematological malignancies. Historically HSCT was the only mode of therapy that could provide a cure for a long list of hematological malignancies including acute myeloid leukemia (AML), acute lymphatic leukemia (ALL), and myelodysplastic syndrome which are the main indications for HSCT in Europe; but also for chemosensitive non-Hodgkin lymphomas (NHL), Hodgkin lymphoma, and multiple myeloma (MM), the main indications for autologous transplantation. However, transplantation could be offered to only a rather small fraction of the patients in need due to the high risk

2531-1379/

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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