UPDATES IN HEMATOLOGICAL MALIGNANCIES

3-4 January, 2020

A commentary of the educational sessions.

A Year 2020 started with a milestone for the Society of Medical Oncology of Pakistan (SMOP) with holding of an international conference on Updates in Hematological Malignancies. Its chairperson, Prof. Zeba Aziz did a commendable job in bringing together eminent national and international speakers on this forum. It was a well-organized and well attended conference with medical oncologists and hematologists from the across the country and distinguished international experts discussing burning topics in latest advances, key management pearls and controversies in treatment of malignant hematological disorders.

First two sessions on day one were devoted to aggressive and indolent lymphomas respectively followed by the session on case presentations and discussion by panel of experts.

Dr. Munira Moosajee from Aga Khan University, Karachi delivered a comprehensive talk on ***Risk adaptive therapy in DLBCL.*** The heterogenous nature of DLBCL was emphasized upon with the 2 subtypes ABC and GCB being important in decision making for appropriate treatment strategy. Pre-treatment prognostication of lymphoma, importance of IPI, Gene expression profile, dual expresser and double hit and triple hit lymphomas influencing the treatment plan was highlighted. While R-CHOP remains the standard of care, Dr. Moosajee elaborated upon the additional role of targeted therapies, immunomodulatory agents which significantly improve the PFS and OS. Speaker also presented the results of various trials using the targeted therapies in combination with immunochemotherapy as first line treatment. Dr. Moosajee elaborated on the data regarding lenalidomide (immunomodulatory agent), mosunetuzumab,a bispecific anti CD20/CD3 antibody, and polatuzumab vedotin (drug-antibody conjugate); Latter, being FDA approved for DLBCL and has been tried with immunochemotherapy for untreated DLBCL producing significantly better responses. Speaker also talked about role of cellular therapies for DLBCL, with its role currently confined in the relapsed and refractory setting.

Dr. Neelam Siddiqui consultant medical oncologist SKMH, delivered a talk on ***CNS prophylaxis in DLBCL.*** Speaker emphasized on the importance of decision making tools such as CNS-IPI for finding out *at risk* patient. In addition, Dr Siddiqui presented data on factors other than the CNS-IPI that aid in risk stratification in our daily clinical practice such as site, number of extranodal sites, morphological subtypes, gene profile with the subtypes of ABC & GCB, dual expresser and double hit dlbcl. This is important to determine as high risk patients have a 22% risk of CNS involvement and should be evaluated for prophylaxis. Integrated risk stratification methods were also elaborated upon. Regarding the route of delivering the treatment, the speaker elaborated on both systemic therapies with high predilection for CNS penetration as well as intrathecal

approaches. High dose methotrexate and cytarabine are the most frequently used systemic agents with high dose methotrexate being the preferred choice due to a favorable toxicity profile. Novel methods to predict CNS relapse were also mentioned such as PET-CT resulting in high total lesion glycolysis, use of pathological markers as ITGA 10, CXR5, NUCLEAR PTEN; PCR investigating micro RNA/ RNU fragments and NGS of cell-free DNA. She elaborated upon the use of novel agents such as lenalidimide, ibrutinib and immune check inhibitors like Nivolumab which can prevent CNS relapse. The talk concluded with some key management points such as watching for late relapses in testicular lymphomas which needs to be translated in to our long term follow up for such patients.

The next session 3 sessions were dedicated to indolent lymphomas. Dr. Kamran Rasheed from Shifa International hospital Islamabad delivered a talk on '***Targeted therapies for Follicular lymphomas'***. The talk started with a brief overview on the natural history, presentation and outcomes of this disease. Treatment goals were also elaborated with the focus of improving progression free survival rather than cure. Dr.Rasheed then discussed in detail about frontline therapies for newly diagnosed follicular lymphoma. He addressed the important question of rituximab vs watchful waiting in asymptomatic FL. He emphasized on wait and watch policy as standard procedure for low risk and low burden disease. He also discussed the controversy regarding rituximab maintenance in the era of PET analysis with recent evidence that it likely not beneficial in early responders. In the realm of relapsed disease, he focused on novel agents and outcomes such as better PFS in combination therapy with lenalidomide and rituximab (AUGMENT). Early relapse (progression in first 2 years) has a high mortality and fact was substantiated with results of different studies. He presented a useful treatment algorithm for early-relapsing follicular lymphoma. He finished his talk mentioning various ongoing trials using novel treatment combinations in FL for which results are still awaited.

Next to speak was Dr. Farrukh Awan from University of Texas-Southwestern in Dallas, USA. He delivered an excellent talk about ***current management of CLL.*** His talk was focused on the current standards of care and its application and implementation in Pakistan. He emphasized that correct diagnosis is not on routine blood counts but on FCM CD23 and CD5 positive cells with a cut of limit of >5000 cells/microliter. Speaker then very nicely addressed the indicators for starting the treatment in CLL patient making it clear that deciding factor is not the lymphocyte count. Instead the treatment initiation is based on stage, disease related symptoms and presence of active disease. He described the CLL-IPI score which includes age>65 years and Binet B/C or RAL 1-4 each with score 1, Beta-2 microglobulin >3.5 mg/dl and IGHV unmutated with score of 2 each and deletion 17p (Fish/TP53 mutation (sequencing) a score of 4. Low , intermediate , high and very high categories thus assigned reveal markedly significant worsening prognosis with the escalating score with 93% and 23% 5 year survival at 2 extremes. Dr. Awan then addressed key pearls in workup with interphase FISH for CLL being the optimum tests required interestingly discouraged the injudicious use of CT scans, FISH and BM test. Dr. Farukh explained that FISH and IGVH are helpful for determining the prognosis and treatment of the disease but even in USA just 55% and 7% of patients respectively get these expensive investigations done. Next, he very succinctly mentioned the pros and cons of chemo-immunotherapy (chlorambucil, FCR, BR). Question of cure in CLL was addressed with results

of CLL10 study where in the group which was FCR treated, the IGHV mutated patients if not recurring in 10 years can be potentially considered as "cured".Dr. Awan strongly recommended BTK inhibitors such as ibrutinib due to its ease of use and impressive 5 year survival at 90%. Excellent responses were seen in the unmutated high risk group. Given the plethora of novel agents such as second generation BTK inhibitors, lenalidmide and venetoclax, the role of first line chemoimmunotherapy is dubious. Lastly, specially focusing on CLL treatment in Pakistan, Dr. Awaan recommended to move away from chemoimmunotherapy , make liaison with pharmaceuticals for trials of third generation BTK inhibitors, bispecific antibodies and CAR-T cells to improve patient care.

Dr. Syed Waqas Imam Bokhari from SKMH delivered his talk on ***role of stem cell transplantation in relapsed indolent lymphoma.*** Speaker explained that SCT for indolent lymphomas is highly contentious due to the presence of highly effective second line therapies now available. He addressed the issue of SCT as primary consolidation in FL and discouraging it as first line setting. This can still be an option in the relapsed/refractory setting. This was highlighted in a case scenario where a patient presented with relapse within 6 months with incomplete response to therapy and high risk at presentation. For local relapse radiotherapy was suggested. Recommended on the basis of various studies that early use of autotransplant should be considered as a treatment option for high risk patients who experience early failure within 2 years of chemoimmunotherapy- which occurs in 20% of FL patients independent of maintenance rituximab. He presented data where those patients who proceed to ASCT within one year of relapse do better than who receive ASCT after 3 or more relapses. He recommended that allogeneic transplant should be best reserved for medically fit patients with highly pre-treated / refractory disease/ those who fail to mobilize stem cell for autotranplant/ patients with disease progression after autotransplant. Allo-transplant can be considered earlier young and fit patient with sibling donor and have failed response to several lines of chemotherapy.Speaker also presented the results of studies comparing allogenic and autologous transplant where an initial decline was followed by significantly better survival was seen when compared to autoSCT. SKMH protocol was shared where autotransplant is done for 2nd relapse in a chemoresponsive patient and sibling allotransplant recommended if patient is in poor risk category with early relapse, chemorefractory disease, in cases of harvest failure, failed several lies of therapy or has post autoSCT relapse.

The lymphoma session concluded with 4 interesting case presentations and the discussion that ensued was very informative and thought provoking. This session was moderated by Dr. Abbas Khokar, Mayo Hospital,

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After lunch, the session was dedicated to acute leukemias. Eminent speakers delivered talks on different aspects and current practices about acute leukemias and bone marrow failure. Dr. Irum Khan Assistant professor from University of Illinois, Chicago talked about ***Treatment updates in Myeloid malignancies***. Prof. Giuseppe Saglio form University of Turin Italy elaborated upon; ***To***

transplant or Not to Transplant in Ph-ve ALL. Prof. Zehra Fadoo from AKU delivered a talk on ***Management of ALL in young adults- A peadiatric oncologist perspective***. This was followed by an eminent speaker, Major Gen Tariq Satti, Chief AFBMT center Rawalpindi who talked about ***Management of Aplastic anemia in Transplant ineligible patients.*** The last 2 talks were for basic medical science were Dr. Nosheen Zahra Zaidi from University of Punjab talked about her research on ***Metabolic crosstalk between leukemia cells and tumour microenvironment***. Professor Amir Faisal of LUMS presented his research - "***A Dual FLT3/Aurora A Inhibitor overcomes D835YMediated Resistance to the FLT3 Inhibitors in Acute Myeloid Leukemia Cells"*** . His lecture was widely appreciated arousing a lot of interest among the audience. His team had an extensive research on molecules which could overcome the resistance to FLT-3 inhibitors for AML patients.

Morning session on day 2 began with the focus of myeloproliferative neoplasms. Dr. Kamran Rasheed talk on ***Polycythemia and Essential thrombocytosis.*** His informative talk started with an account of evolution of WHO diagnostic criteria for PV and ET. Dr. Rasheed talked about the driver mutations in MPNs where JAK 2 mutations are universally present. Thrombosis being the major cause of mortality, the speaker emphasized on thrombosis risk-adjusted management. Regarding management, Dr. Rasheed favoured peg interferon over hydroxyurea for better molecular response. The speaker substantiated by referring to various studies where peg interferon was used as first line treatment. ELN criteria for hydroxyurea resistance and intolerance were clearly elucidated. The next focus of the talk was indication and use ofJak2 inhibitors such as ruxonilib. To conclude, he presented the both the NCCN and the ELN guidelines for management of these patients.

Prof. Giusepe Saglio, a world leader in CML, delivered his talk on ***current trends in treatment of CML***. His talk started out a historical perspective with the Iris study where imatinib as a first line treatment resulted in a 80% overall survival. The study emphasized that all treatments must achieve 80% deep molecular response (DMR). Issue of intolerance or delayed response to imainib was addressed with second generation TKI (2G-TKI)where switching to 2G-TKI gradually improves the molecular response. Speaker then addressed the question of starting 2G-TKI in first line. With reference to a study, the cumulative DMR was high with nilotinib compared to imatinib in a 5 year analysis. Prof. Saglio talked about treatment discontinuation and mentioned the importance of documenting a one log reduction after 3 months of starting treatment as an indicator or survival. He explained that MR 4.5 means a reduction of 4.5 log which was previously called CR. Speaker also compared the ENEST free and ENESTop studies highlighting strongly that importance of molecular response achieved as the best indicator of residual disease present and a major determinant of the chances of a successful TFR independent of TKI used. It is important to achieve a fast response initially since this an indication of low residual recurrent clone in the patient. Speaker strongly emphasized that currently the target of CML therapy is to achieve the deep molecular response as soon as possible in the highest percentage of CML patients so as to discontinue the therapy and achieve "operational cure".

These talks were followed by a session of case presentations and discussion by the panel of experts. Cases of myelofibrosis, CML and a case of NHL+CML were presented from different

hospitals and it highlighted the challenges of management of MPNs in a low middle income country

Session II was devoted to challenging haematopathology cases by Dr. Imran Nazir from Shifa International Hospital, Islamabad. It was a highly informative and interactive session beneficial to both faculty and trainees. Speaker began with the basics of histopathological diagnosis of haemopoietic malignancies. Emphasis was made on type of tissue, architecture followed cytological details of the tumour as well as the background cells. The next point of discussion was on the indications and limitations of IHC and the need for molecular techniques in reaching at a conclusive diagnosis in hematological malignancies. Dr. Imran stressed on the importance of FISH and/or molecular tests for determining rearrangements, translocations and rearrangement of important gens that determine prognosis such as myc, BCL, BCL6. He very elegantly explained dicordance between expression as determined by IHC expression and correlation for rearrangement by FISH and its impact on prognostication. This introduction was followed by interesting and challenging cases presented as microphotographs where he extensively interacted with audience for diagnosis.

The last session of the conference was devoted to multiple myeloma with a well thought of sequence of relevant topics. Dr. Muhammad Arif, consultant haematologist oncologist from Doctors Hospital, Lahore delivered his talk on ***management of MM in transplant eligible patients.*** He addressed the important aspect of pretreatment evaluation. Clonal evolution and progression of myeloma with acquired mutations was highlighted. Risk stratification was explained with importance of high risk and ultrahigh risk myeloma showing suboptimal response to treatment. Various factors determining the transplant eligibility were also highlighted. Speaker stressed that according to updated guidelines on determination for eligibility for transplant with increasing age is no longer the sufficient criteria ineligibility. Additional patient and disease related factors need have to be taken into consideration. He clarified that declining renal function/ dialysis is not a contraindication. Dr. Arif explained that initial therapy with triplet drugs x3-4 months followed by Stem cell collection as being the standard of care. Speaker supported the role of ASCT as it gives much better survival than systemic therapy alone. He also talked about the role of tandem transplant in certain patients where there might still be indicated. He emphasized upon the significance of maintenance therapy considering relapse inevitably occurs after transplant. The speaker referred to NCCN combo regimen for primary induction therapy where the option is bortezomib/lenalodomide/dexamethasone or bortezomib/cyclophosphamide/dexamethasone (renal insufficiency patients). Speaker then elaborated upon the FDA approved daratumumab where a combination therapy of DVTd proved to have a better PFS. So future is now four drugs may become the standard of care.

Next was a highly informative talk by Dr. Munira Moosajee on ***Management of MM in transplant ineligible patients.*** The speaker considered it a challenging situation especially in Pakistan where the continued therapy will have issues with cost and compliance. She elaborated in detail the eligibility criteria going into depth of factors like frailty; explaining the Frailty Scale in detail. Talking about the frontline treatment in ineligible patients' speaker emphasized the importance of obtaining a deep response as a goal of therapy in this group of patients. She

discussed that addition of novel agents improves the survival and better PFS as with daratumamb. Practice pearls included cautioned against the use of lenalidomide in impaired renal function, dose adjustment in the frail population and using the alternate formulation particularly of bortezomib to decrease toxicity Speaker also talked about some new enrolling trials which recommended 3 drug combination as the first line treatment. Dr. Moosajee elaborated upon the important aspect of supportive care for management of bone disease essential for symptom management. Importance also needs to be given to myelosuppression, infection control and vaccination. Lastly speaker referred to Mayo clinic protocol in 2020 for frontline management of MM wherein recommendation for transplant ineligible newly diagnosed myeloma patients is VRD x 9 months or DRD followed by maintenance therapy.

The session ended with a highly interesting talk by Dr. Ayaz Mir from Shifa International hospital, Islamabad on a very practical topic: ***Treatment options in relapsed MM in a resource constrained country***. Dr. Mir highlighted the diagnostic tests required to establish the diagnosis. He stressed that a mere numerical increase in plasma cells in bone marrow is nonspecific and not diagnostic for MM. Clonality of plasma cells as determined by kappa and lambda restriction, serum electrophoresis and M protein quantification and free light chain assay are the pre requisite. He very suggested on foregoing nonessential investigations at the time of relapse such as B2-macroglobulin, repeated IFE testing on serum and urine when M protein is quantifiable and bone marrow biopsies which add cost to the treatment. He also suggested that expensive tests like MRI or PET scan may not be needed except for MGUS, SMM and non-secretory MM. Talking about the treatment options available in limited resources, Dr. Mir talked about standard treatment options and modifications as per patient's financial challenges. Supportive care modifications such as zolendoric acid q x 3 months x 2 years and bortezomib SQ vs. IV can result in considerable cost saving measures. His talk had very useful take home messages stressing effective diagnostic and monitoring tests, treatment combinations and role of stem cell transplant.

The day ended with an interesting case presentation of recurrent bladder mass which histologically proved to be isolated amyloidosis. The case was actively discussed by the audience and panel of experts.

The organizing committee also recognized the importance of mentoring of trainees. Therefore, a first of its kind mentoring sessions were slotted on both days of the meeting as well as a one on one session regarding pitfalls and tips on the FCPS exam. These sessions were very well attended by the residents where not only they were able to talk about challenges and stressors of training but also advice regarding their future career goals.