MultipleMyelomaHub

General MM

2017 ASCO Annual Meeting: Are we integrating biologic advances in MM into clinical practice?

Devona Williams | Jun 07, 2017

The Multiple Myeloma Hub was happy to attend the 2017 ASCO Annual Meeting held in beautiful Chicago, Illinois at McCormick Place. Thousands of oncology professionals attended and shared dynamic insights from cutting edge research. The Myeloma Hub team is pleased to share data from the education session covering molecular advances in myeloma and implications for its use in daily clinical practice.

Professor Gareth Morgan from University of Arkansas led with an introductory talk about the integration of genomics and treatment. He spoke about the clonal evolution and expansion of myeloma cells, which leads to more advanced disease processes over time. In addition, there is also co-evolution of the disease in the microenvironment over time. Because of the vast changes that take place in myeloma cells during the process of disease progression, there are many opportunities to integrate genome information into improved treatment outcomes.

One method is to modify individual therapy and future clinical trials based on risk stratification. Tools in this venture include reference to the revised ISS staging, FISH analysis, gene expression profiling and DNA driver based therapy. The Myeloma Genome Project is working to develop and enhance the power of risk stratification, by defining genetic markers able to detect more aggressive disease, in an effort to better modify therapy.

Mutational directed therapy will help to define drivers of disease progression and lead to personalized therapy plans. For more personally directed therapy, interpretation of the mutational landscape of myeloma must be recharacterized. Instead of focusing solely on mutation translocations, genetic information must also be considered. Because drug therapy applies selective pressure, the most effective approach is to focus on downstream targets. Instead of broad based targets which are upstream in disease pathology, such as the RAS pathway, acquired mutations, secondary translocations and epigenetic modifications, modification based on targets that drive disease early in the pathologic process, such as hyperdiploidy and primary translocations, will lead to better responses.

Precision immunotherapy can help overcome the problems of inconsistent mutations and loss of heterozygosity, the latter of which is more common in relapsed/refractory myeloma and is correlated with worse outcomes. Novel immunotherapy is directed towards actionable mutations, such as BRAF, MEK and BCL2. Also, antibodies, checkpoint inhibitors, CAR T-cells and vaccines are innovative approaches to immunotherapy. Together with agents that target plasma cell biology, such as proteasome inhibitors, immunomodulatory drugs, steroids and alkylating agents, the landscape of treatment can be advanced.

A clinical controversy about application of minimal residual disease (MRD) use in clinical practice was debated by Professor Xavier Leleu and Professor Sagar Lonial. Professor Leleu presented the case for relevance of MRD as an endpoint. The evaluation of myeloma therapy success has evolved over time. Formerly acceptable goals of therapy were VGPR, then CR. However, the question remains as to whether CR is a successful measure of therapy if patients have a very short time interval to disease relapse.

The measurement of CR and depth of CR make a big difference in terms of PFS and OS. CR implies no clonal myeloma cells are measured in serum and urine, although there may be residual tumor in bone marrow. CR may equate to clonal detection of 10^{10}, and MRD correlates to detection at 10^{-4} or lower. The depth of CR has an impact on time to relapse and survival. IFM study data reported MRD after maintenance therapy as 10^{-4} to 10^{-6}, which is a wide range. Time to relapse for patients with an MRD of 10^{-4} was 18 months, compared to greater than 48 months for patients with an MRD of 10^{-6}.

While stating this is a relevant endpoint, Professor Leleu acknowledged several uncertainties, such as at what point during therapy is the optimum time for MRD testing. There is currently no standard recommendation for the timing of the test. Also, there are some patients who will never truly destroy all clones, but will still proceed to a MGUS-like profile. For this group, it is best not to pursue MRD status, as they will require intensive chemotherapy, which may cause more harm than benefit. Another uncertainty is the choice of sampling method to enable MRD testing. Traditional methods of bone marrow aspiration or biopsy can lead to a misdiagnosis if the sample area does not contain a relapsed clone. Use of PET CT for measure of MRD may be a better tool, as patients who are MRD negative per bone marrow, but positive per PET CT have poor outcomes. This suggests clonal positivity in an area that was not sampled, leading to poor prognosis. The last point of uncertainty is that MRD does not yet give us information for adapting therapy decisions, but it is hoped that upcoming clinical trials will help to make this determination.

Professor Sagar Lonial offered a counterpoint discussion that MRD is not yet ready for daily clinical practice. He was in agreement that useful data can be derived from the test, but feels that it is not an appropriate routine test for every patient. One of the points he shared was that there is no consensus on what value represents actual MRD. A value of 10^{-5} is the usual standard for flow cytometry, however, all MRD testing methods do not have the same sensitivity. Results are not interchangeable across different methods. There is also no consensus about optimal timing. MRD rates may change based on performing the test pre- or post- stem cell transplant or during prolonged maintenance therapy. As far as daily decision making, MRD does not give an indication of when it is advisable to stop therapy. Taking into consideration the potential for sampling errors, inconsistencies with sensitivity across methods, and the lack of consensus about sampling time, MRD testing remains a great tool for clinical trials, but should not currently be indicated for routine clinical practice.

Professor Irene Ghobrial shared information about novel biomarkers in myeloma. She stated that currently used prognostic biomarkers include bone marrow biopsy, blood sampling and imaging, but felt there are opportunities to modernize the use of all these methods. She also touched upon the topic of the vast genomic complexity that occurs in myeloma such that a patient will have many different clones by the time a diagnosis is made.

Professor Ghobrial communicated that novel approaches to MRI include the identification of focal lesions of disease and patients that will relapse. PET/CT may be used in a manner to determine prognosis after treatment. Blood biopsies are primed for the next era of biomarker application in myeloma. Moving beyond M-spike and light-chain monitoring of disease burden. Innovative options include measuring cell free DNA, measuring peripheral circulating tumor cells and whole exome sequencing. Data from whole exome sequencing has indicated that the same clones are present in the bone marrow as peripheral blood. This multifaceted approach can help patients who are at the highest risk of progression and resistance to therapy. These presentations represent an exciting era for myeloma treatment and will undoubtedly change the outlook for the better.

References

1. 2017 ASCO Annual Meeting, EDUCATION SESSION, Monday, June 5th 2017: Are We Integrating Biologic Advances in Multiple Myeloma into Clinical Practice? Chair: Irene M. Ghobrial, MD, Dana Farber Cancer Institute/Harvard Medical School. Speakers: Gareth John Morgan - Myeloma Institute, University of Arkansas for Medical Sciences; Xavier Leleu - CHU de Poitiers; Irene M. Ghobrial - Dana Farber Cancer Institute/Harvard Medical School; Sagar Lonial - Winship Cancer Institute.