MultipleMyelomaHub

General MM, Relapsed/refractory patients

2017 ASCO Annual Meeting: Treatment of relapsed MM in the era of novel drugs

Devona Williams | Jun 04, 2017

The Multiple Myeloma Hub were delighted to attend 2017 ASCO Annual Meeting held in beautiful Chicago, Illinois from June 2nd to 6th, at McCormick Place. Data were presented in many scientific sessions and clinical trial abstracts. All aspects of cancer research and care were covered. The Myeloma Hub team is pleased to summarize key findings of the session Treatment of Relapsed Myeloma in the Era of Novel Drugs.

The session began with Professor Nina Shah from the University of California, San Francisco presenting the concept that relapse is not defined by one homogeneous set of criteria for myeloma patients. Relapse may be defined in terms of an increase of biochemical markers or by worsening of clinical symptoms. Patients with progression of CRAB symptoms (increased calcium, renal failure, anemia and, bone lesions) are a population that require early treatment for relapse. Subsets of patients with biochemical relapse features who require early treatment intervention are those with aggressive clinical disease, patients with a short treatment free interval, patients with imminent risk of significant organ dysfunction and those with unfavorable cytogenetics.

There are several gray areas for early treatment initiation at relapse. For patients who have been doing well on maintenance therapy, the physician may closely follow values for changes in M proteins to help with the decision to start additional therapy. Patients who have an increase in light chains, multi-refractory disease, or smoldering myeloma, may benefit from early treatment initiation. Achievement of negative MRD and then relapse with positive MRD is a debatable population which may benefit from early therapy at relapse. For individuals with poor performance status and only chemical relapse, physicians must be very cautious about assessing the risk of additional pharmacotherapy.

In general, treating myeloma relapse with further drug therapy is not always warranted. The decision to proceed must be evaluated carefully by considering the magnitude of disease progression, clinical symptoms of the patient and the overall risk status and the patient's disease. For individuals with poor performance status and relapse, not giving additional therapy is a valid option in many cases.

Professor Laurent Gardaret from Hospital Saint-Antoine in Paris gave an excellent talk about weighing the options of triplet versus doublet therapy for myeloma relapse. The standard recommendation for relapse is to treat patients using triplet drug therapy, however, there are certain subsets of patients where doublet therapy is preferred. With the goal of balancing efficacy and toxicity, it is important to prescribe regimens containing varied mechanisms of action while avoiding overlapping drug toxicities.

There are several clinical trials which compare triplet to doublet regimens. An IFM trial compared bortezomib, thalidomide, dexamethasone (VTD) triplet to thalidomide, dexamethasone (TD) therapy. The results showed clinical benefit with an improvement in progression free survival and overall survival, however the triplet therapy group experienced greater dose dependent toxicities. Comparison trials of lenalidomide and dexamethasone (Rd) in studies adding either carfilzomib,

ixazomib, elotuzumab or daratumumab, have all shown a benefit for triplet therapy over doublet regimens. Adding daratumumab to bortezomib and dexamethasone (Vd) led to an increase in progression free survival in both POLLUX and CASTOR trials.

Doublet therapy may be preferred for frail patients, patients with significant comorbid medical conditions, such as renal impairment or neuropathy, and those with high risk disease. For determination of frailty of patients, the International Myeloma Working Group (IMWG) has developed an assessment to determine if patients meet the definition of frail or fit. Frail patients need adjustment to receive less aggressive therapy regimens. Frail patients have higher rates of therapy discontinuation with triplet therapy. If triplet therapy is stopped too early, then patients may lose the benefits of the three-drug combination. Patients with substantial organ dysfunction or neuropathy can benefit from doublet therapy to limit toxicity. Lastly, patients with poor cytogenetics and high-risk disease may benefit from using two drugs at initial relapse, to enable more options if additional therapy is needed in the future.

Following this, Professor Shaji Kumar from Mayo Clinic spoke about sequencing of therapy for relapsed myeloma. With novel therapy successes, sequencing is becoming more important due to increases in time to relapse. Recent data for median time to relapse is 3 to 4 years for myeloma patients. Considerations about choosing the sequence of therapies are imperative for many reasons. As patients may now have multiple relapses, physicians now have a better understanding of the biology of relapse. Therefore, with the advent of many exciting novel agents, a discussion regarding the right sequence of treatment, based on the individual patient profile, is a very relevant topic.

Understanding the biology of relapse is vital as each subsequent drug exposure leads to a decrease in response and shorter duration of time to succeeding relapses. The decrease in response is explained by clonal evolution in myeloma cells. For patients with multiple relapses, the original disease clone continues to change with exposure to new therapies.

Considerations for choosing subsequent therapies include determination of refractory status to prior therapies and patient preferences. The refractory status of disease will help determine whether to use the same regimen for additional treatment or if a change in drugs is warranted. If initial therapy was not refractory to bortezomib or lenalidomide, then subsequent cycles can use the same regimen. For patients who are refractory to bortezomib or lenalidomide, adding different agents in the same class, such as carfilzomib or pomalidomide, has led to better outcomes. In addition to changing the medication in the same class, the addition of daratumumab has also led to excellent treatment outcomes.

Specific cases which require special guidance for therapy sequencing are patients with bulky disease, extramedullary disease and secondary plasma cell leukemia. VDTPACE may be used for patients with secondary plasma cell leukemia or with bulky disease at relapse, as a bridge therapy to stem cell transplant. Patients with extramedullary relapse have poorer outcomes, which necessitates high dose treatment with anthracyclines and alkylator agents.

This session summarized several important principles of treating relapse. The duration of initial response and drugs used to achieve initial response are key. These factors determine the intensity and choice of agents to prescribe for subsequent relapses. The performance status and underlying medical comorbidities are an indication of which drug toxicities will be well tolerated to maintain therapy cycles and reach maximum clinical outcomes. Patient specific therapeutic goals and preferences help to determine agents and optimal routes of administration for therapies, for parenteral or oral therapies. Lastly, the characteristic of relapse, whether it is bulky disease, extramedullary or a plasma cell leukemia all highlight the fact that treating relapse in myeloma is not a “one size fits all” approach.