Review Article

Multiple myeloma: Looking beyond standards

ABSTRACT

Multiple myeloma has been regarded as an incurable disease with frequent relapses. The diagnostic criteria have been revised multiple times to include early stage of the disease where treatment can be effective and can prolong the survival. Newer diagnostic criteria for myeloma have incorporated ≥60% plasma cells in the bone marrow and serum free light chain ratio (involved to uninvolved free light chains) of ≥100. The role of positron emission tomography-computed tomography scans has been recognized, and it has been increasingly utilized upfront in the management of multiple myeloma. Role of minimal residual disease monitoring has been studied in multiple trials and will in near future guide the treatment. Autologous stem cell transplant is still the preferred consolidation therapy after initial three or four drug induction. With the use of novel drugs combinations and with emerging treatment options the standard of care of myeloma patients will change.

Key words: Multiple myeloma; novel agents; stem cell transplant

Introduction

Over the last 15 years, there has been a paradigm shift in the management of multiple myeloma. Not only have the treatment options increased but also the need for keeping a low threshold to treat high-risk smoldering myeloma has emerged. Treatment has become more potent and better tolerated. The role of advanced imaging such as positron emission tomography-computed tomography (PET-CT) scans and magnetic resonance imaging (MRI) has been recognized, and they are being increasingly utilized in the management of multiple myeloma. Newer laboratory-based techniques have emerged for better prognostication, and the concept of minimal residual disease (MRD) in multiple myeloma is being actively investigated. The next generation immunomodulators and proteosome inhibitors are also being increasingly utilized. However, autologous stem cell transplant (ASCT) is still considered the standard of care for eligible patients and is being offered to older patients as well. With a number of recent advancements in this remitting relapsing disease, the hope for long-term disease control and perhaps cure has been rekindled.

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Updated Diagnostic Criteria

Diagnosis of myeloma is unique among hematological malignancies in that it has both clinical and pathological aspects to it. The previous disease definition necessitated end organ damage to qualify as symptomatic multiple myeloma which required treatment.[1] With newer effective and less toxic therapies, this dogma has recently been challenged.[2] This has been recognized by the International Myeloma Working Group in the revised diagnostic criteria.[3] In addition to the traditional definition of the combination of a clonal plasma cell disorder and end organ damage as defined by "C = Calcium (elevated), R = Renal failure, A = Anemia, B = Bone lesions (CRAB)" criteria, three biomarkers have been

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identified whose presence could diagnose myeloma in the absence of overt end organ damage. The presence of any one of these predicts for over 80% likelihood of conversion to overt myeloma over 2 years. Such a high probability has been felt to justify classification of these patients as myeloma and to start myeloma directed therapy.

The first such biomarker is the presence of ≥60% plasma cells in the bone marrow. This cut-off was chosen on the basis of a report by Rajkumar *et al*., showing >95% of such patients progressing to myeloma within 2 years.[4] The second biomarker is serum free light chain ratio (involved to uninvolved free light chains) of ≥100. In a retrospective analysis, the risk of progression to myeloma in the first 2 years in such patients was found to be 72% by Larsen *et al*.[5] The third myeloma defining biomarker is the presence of >1 focal lesion on MRI (at least 5 mm in size). Two studies have shown that about 70% such patients will progress to myeloma over next 2 years.[6,7]

There are a few other biomarkers which have been found to predict for a significant risk of progression. These include high levels of circulating plasma cells, abnormal plasma cell phenotype with immunoparesis, certain cytogenetic abnormalities (*t*[4:14], 1q amp, del17q), and high bone marrow plasma cell proliferative rate. However, their inclusion into formal diagnostic criteria awaits further study.[3]

Incorporation of Advanced Imaging Techniques

Bones are the most frequently affected organ in myeloma, affecting about two-third of patients at presentation and frequently associated with severe morbidity and adverse quality of life.[8] Whole-body skeletal surveys have been used for a number of years for diagnosis of myeloma bone disease. This technique has a number of limitations. It has been shown that a lytic lesion becomes obvious on X-ray only after 30–50% loss in bone mineral density.[9] Its sensitivity is particularly limited in the spine and sternum where it frequently fails to distinguish between myeloma-related bone disease and age-related osteoporosis.[10] Over the last 10 years, modern imaging techniques of CT, MRI, and PET have been used and found to be more sensitive than plain X-rays.[11] The most recent diagnostic criteria include use of any of these techniques in two important ways. For one, a diagnosis of smoldering myeloma cannot be made without the use of one of these techniques to exclude the presence of bone disease. Second, while the previous criteria were somewhat ambiguous on the use of advanced imaging, the most recent version accepts bone disease on advanced imaging as myeloma-related organ damage. PET-CT and MRI have been found to be overall similar in sensitivity.[12] PET-CT has the advantage of having a functional component by virtue of use of fluorodeoxyglucose (FDG). Availability of resources and expertise will likely determine the use of any one of these techniques in a given setting.

Revised International Staging System

It is recognized that myeloma is a heterogeneous disease with patient survival durations ranging from a few months to many years. There are a number of markers that have been identified as being predictive of patient outcomes ranging from simple laboratory tests such as lactate dehydrogenase (LDH) to cytogenetic markers to genome-wide analysis. In 2005, the International Staging System (ISS) devised a simple prognostic tool incorporating albumin and beta-2 microglobulin and has been used widely.[13] Recently, there has been an attempt to improve upon this model by incorporating interphase fluorescence *in situ* hybridization analysis and LDH, so as to incorporate disease biology into prognostication. The revised-ISS (R-ISS) was developed using a large database of 3060 myeloma patients.[14] The high-risk cytogenetic abnormalities included were del17p, *t* (4:14), and *t* (14:16). R-ISS Stage 1 includes ISS Stage 1, no high-risk cytogenetics and normal LDH; R-ISS Stage 3 includes ISS Stage 3, high-risk cytogenetics and/or high LDH; R-ISS Stage 2 includes all the remaining conditions. The predicted 5-year overall survival (OS) for R-ISS Stage 1, 2, and 3 was 82%, 62%, and 42%, respectively. Although R-ISS is an improvement on the previous ISS and quite pragmatic, it does suffer from several limitations. These include noninclusion of abnormalities of chromosome 1, patient factors such as age, performance status, and majority of patients being <65 years of age and lack of a validation cohort. In the future, molecular techniques such as genome expression profiles and single nucleotide polymorphisms could come to play an important role in prognostication once they are better understood and become more widely available.

Minimal Residual Disease

The concept of MRD in hematological malignancies has been around for a long time. The importance of measuring it and incorporating successfully into the treatment algorithm has been best demonstrated in acute lymphoblastic leukemia. There has been an increasing interest and greater advancement in measuring MRD in myeloma in the last 5 years. We briefly discuss some of the involved techniques and their relative advantages and disadvantages.

1. Multiparameter flow cytometry (MFC): Simultaneous measurement of at least eight markers and evaluation

of a greater number of cells has increased the sensitivity of MFC, allowing better separation of aberrant clonal plasma cells from normal plasma cells. With these modern MFC-MRD techniques, the sensitivity has increased to 10^{-5} – 10^{-6} (sensitivity defined as minimal percentage of cells defined within or out of the range of the quantitative method). The technique is the most widely studied among myeloma-MRD techniques as demonstrated by a large number of recent publications on it.[15,16] It has several potential advantages. It is applicable to all patients, is available worldwide, is relatively cheap with a rapid turnaround time of 2–3 h. There have been greater efforts to standardize it to minimize interlaboratory variability such as the EuroFlow/Myeloma Research Foundation (MRF) (see EuroMRD.org). One major disadvantage is the need for a fresh bone marrow sample since peripheral blood samples have not been found to be sensitive. As such patchy involvement of the marrow can impact the results and it does not take account for extramedullary disease

2. Molecular techniques: These include allele-specific oligonucleotide polymerase chain reaction and next generation sequencing of immunoglobulin genes. These techniques are based on the principle that rearrangement of heavy and light chains (V, D and J) created random insertions and deletions at junction sites of V, D, and J chains, creating a "fingerprint-like" pattern for each mature B cell. Although these techniques are highly sensitive, they also suffer from some disadvantages. The techniques are not as widely available as MFC, especially in the developing world, a baseline sample is absolutely required and the turnaround time is in the range of 5–7 days. Like MFC, these techniques also require a bone marrow sample and do not represent extramedullary disease
3. PET-CT has a great advantage over lab based MRD monitoring techniques in that it overcomes the issue of patchy bone marrow involvement and identifies extramedullary disease.[17] The functional data provided by FDG uptake is complemented by the images from the CT component. It also has the advantage of wide availability, immediate turnaround time and there is no need for a baseline study. However, both false positives and false negatives have been reported with co-existing infectious and inflammatory conditions.[18]

Although a number of studies have shown the role of MRD detection in prognosticating myeloma patients, there is to date no study showing improved patient outcomes related with MRD-guided treatment algorithms. Although complete remission and MRD-negative status is felt to be desirable in all hematological malignancies, it has been shown that around 10% of myeloma patients can achieve long-term disease control and survival without achieving complete remission.[19] A number of current studies have incorporated MRD assessments in their protocols and may shed more light on the matter and might recognize subsets of patients where targeting MRD negativity could be of particular interest, such as patients with high-risk cytogenetics.

Treatment

Overall survival (OS) in myeloma has improved significantly in the last decade with the emergence of thalidomide, bortezomib, and lenalidomide. Recently, carfilzomib (a new proteasome inhibitor) and pomalidomide (a new thalidomide analog) have been approved for the treatment of multiple myeloma.

As for treatment is considered, myeloma patients can be divided into those who are fit for transplant and those who are unfit for transplant. This division is based on organ function and overall performance status. At present, the standard of treatment is to give initial induction therapy with three to four drugs combination followed by autologous stem cell harvest and transplant in patients eligible for auto ASCT. In patients who are not eligible for transplant because of comorbidities, the treatment is continued till the best response is achieved followed by either no treatment and wait and watch particularly in those patients with complications related to treatment or to give maintenance therapy who tolerate the initial treatment well. Age, *per se*, is not a contraindication for transplantation, as myeloma is a disease of elderly people though it can affect young people as well. Those patients who are fit for high-dose chemotherapy and autologous transplantation are given an induction therapy followed by high-dose chemotherapy, usually melphalan and autologous stem cell rescue.[20] Patients are usually treated with about three to four cycles of induction therapy prior to stem cell harvest. After harvest, patients can either undergo upfront ASCT or resume induction/maintenance therapy and considering ASCT after the first relapse.

Three-drug regimens including bortezomib such as bortezomib-cyclophosphamide-dexamethasone (VCD), bortezomib-thalidomide-dexamethasone (VTD), and bortezomib-lenalidomide-dexamethasone (VRD) are highly effective in newly diagnosed multiple myeloma. VCD has significant activity in newly diagnosed multiple myeloma and is less expensive than either VTD or VRD. However, recently the triplet VTD induction therapy was shown to

be associated with significantly higher complete response (CR) and very good partial response rates compared to VCD.[21,22] The neurotoxicity of bortezomib can be greatly reduced by administering bortezomib once a week instead of 2 times a week, and by changing the administration route from intravenous to subcutaneous. About half of myeloma patients experience renal insufficiency at some point in the disease course. Although no particular drug combination has been shown to be superior to others in such patients, outcomes have improved in the era of novel agents.[23] Rapid institution of therapy to prevent irreversible renal damage is vital. Bortezomib is highly efficacious and has the best safety profile in such patients. Fifty-nine percent of patients presenting with renal insufficiency and treated with a combination of bortezomib and dexamethasone had a renal response at a median of 11 days.[24] Cyclophosphamide can be added to this combination to increase the response rate making VCD an attractive regimen for such patients. Lenalidomide can also be used as long as the dose is adjusted and patients and closely monitored for myelosuppression.

ASCT should be considered in all eligible patients.[25] At present, allogeneic transplantation as frontline therapy should largely be considered investigational. ASCT has been shown to improve median OS in multiple myeloma by approximately 12 months.[26,27] However, trials have shown that OS is similar whether ASCT is done early (immediately following four cycles of induction therapy) or delayed (at the time of relapse as salvage therapy).[28]

Almost all patients with multiple myeloma eventually relapse. The remission duration in relapsed myeloma decreases with each regimen and the disease ultimately becomes refractory and progresses. The median progression-free survival (PFS) and OS in patients with relapsed myeloma refractory to lenalidomide and bortezomib are poor.

Next generation novel agents

Carfilzomib is a novel keto-epoxide tetrapeptide proteasome inhibitor recently approved for the treatment of relapsed refractory myeloma in patients who have been previously treated with lenalidomide and bortezomib. Pomalidomide is an analog of lenalidomide and thalidomide and has been approved for the treatment of relapsed refractory myeloma patients failing lenalidomide. The response rate of these agents in patients refractory to lenalidomide and bortezomib has been in the range of 16–49%.[29,30]

Emerging treatment options

Other recently approved agents include panobinostat, a histone deacetylase (HDAC) inhibitor, the anti-CD38 monoclonal antibody daratumumab, and elotuzumab, an anti-CS-1 monoclonal antibody.

Panobinostat is the first HDAC inhibitor approved to treat multiple myeloma. This was on the basis of PANORAMA-1 study, which was a multicenter, randomized, double-blind study, comparing bortezomib/dexamethasone to panobinostat/bortezomib/dexamethasone. With a median follow-up of 6.4 months there was a significant improvement in the PFS in the panobinostat arm (11.99 months [95% confidence interval (CI) 10.33–12·94] vs. 8.08 months [7.56–9.23]; hazard ratio 0.63, 95% CI 0.52–0.76; $P < 0.0001$]).[31] Common adverse events noted in the study arm were thrombocytopenia (67%), lymphopenia (53%), diarrhea (26%), and asthenia (24%). It is intended for patients who have received at least two prior standard therapies, including bortezomib and an immunomodulatory agent.

Elotuzumab was approved on the basis of ELOQUENT-2, a randomized phase 3 study, comparing lenalidomide/dexamethasone to elotuzumab/lenalidomide/dexamethasone.[32] The rate of PFS was significantly different at 2 years (41% vs. 27%) in favor of the elotuzumab arm. Daratumumab, another recently approved drug, is an anti-CD38 monoclonal antibody which has shown remarkable activity as a single agent in heavily pretreated subjects. In the recently reported SIRIUS study, the overall response rate was 29.2% with three patients achieving a stringent CR.[33] Of note these patients had received a median of five lines of prior therapies, 80% had received a prior ASCT, and 95% were refractory to the most recent proteasome inhibitor or immunomodulatory drug (IMID).

Ixazomib is the first oral proteasome inhibitor to receive Food and Drug Administration approval. It has shown activity in combination with lenalidomide in both newly diagnosed and relapsed/refractory disease.[34,35]

Supportive Care

As discussed before, bones are the most frequently affected organs in myeloma, affecting about two-third of patients. Bisphosphonates form the cornerstone of bone-directed therapy in myeloma. They have been shown to decrease skeletal-related events, improve pain score, and improve the quality of life. In the Medical Research Council myeloma IX trial zoledronic acid was compared to oral clodronate and remarkably showed a benefit in OS in the zoledronic acid arm indicating that bisphosphonates could have an anti-myeloma effect as well.[36] Denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand has also

been studies for bone disease in myeloma. In a head to head trial of zoledronate and denosumab, although the incidence of skeletal-related events was similar, survival was inferior in the denosumab arm.[37] More studies to clarify the role of denosumab for myeloma bone disease are underway. Other aspects of supportive care such as prophylaxis against venous thromboembolism, infectious disease prophylaxis remain important as well.

Conclusions

With the broadening definition of myeloma patients who will be requiring treatment in the future along with the increasing burden of relapsed/refractory myeloma patients, more and more newer agents will be required to tackle the menace of myeloma. The novel agents including IMIDs and proteasome inhibitors represent the main treatment in this setting as of now. There are trials in progress to incorporate the monoclonal antibodies to the upfront setting with other agents, something akin to the R-CHOP protocol for lymphoma. In the near future, as we start to treat myeloma patients sooner in their disease course with multi-agent protocols, incorporating ASCT along with prolonged consolidation/maintenance plans and advanced techniques to monitor MRD, perhaps we can actually cure some proportion of these patients. Furthermore, the developing world will likely continue to face unique challenges, involving younger patients with advanced disease at presentation and nonavailability of most of the newer therapies.

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Conflicts of interest

There are no conflicts of interest.

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