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A New and Evolving Era in Multiple Myeloma Field

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Abstract

Multiple myeloma (MM) is one of the most common hematologic disorders in US, which accounts for approximately 15% of hematologic malignancies [1]. The American Cancer Society estimates that about 30,330 people will be diagnosed with multiple myeloma and about 12,650 will die of the disease in 2016 [1]. The number of people diagnosed with MM has been increasing over the past ten years, fortunately, with the deeper understanding of the disease and advances in treatment and research, more novel therapeutic classes have been granted FDA approval and incorporated into treatment leading to treatment paradigm change and significantly improved patients' survival [2]. To address recent discoveries about the molecular pathogenesis of the disease, International myeloma working group (IMWG) has updated diagnostic criteria and staging system for Multiple myeloma [3,4]. Recently National Comprehensive Cancer Network (NCCN) has updated its guideline to reflect rapid progress in the management of multiple myeloma [5]. The purpose of this review is to highlight some of most recent changes and significant progress in multiple myeloma clinical practice from basic disease definition changes to the advancement of therapeutic options including most recently FDA approved anti-myeloma agents as well as some promising novel therapeutic approaches under clinical development.

Keywords: Multiple myeloma (MM); Revised international staging system (R-ISS); Minimal residual disease (MRD); Risk stratification; Novel therapeutics; Immunotherapy

Abbreviations

MM: Multiple Myeloma; MRD: Minimal Residual Disease; CR: Complete Response; OS: Overall Survival; PFS: Progression Free Survival; TTP: Time To Progression; NGS: Next-Generation Sequencing; CDC: Complement Dependent Cytotoxicity; ADCC: Antibody-Dependent Cellular Cytotoxicity; BCMA: B-cell Maturation Antigen; CRS: Cytokine Release Syndrome; FISH: Fluorescence In Situ Hybridization; R-ISS: Revised International Staging System; PD-1: Programmed T cell death 1; PD-L1: Programmed Death-Ligand1; HDT/ASCT: High-Dose Therapy/Autologous Stem Cell Transplantation; NCCN: National Comprehensive Cancer Network; IMWG: International Myeloma Working Group; MFC: Multiparameter-Flow-Cytometry; CRd: Carfilzomib Combined with Lenalidomid and Dexamethasone; ERd : Elotuzumab in combination with Lenalidomide and Dexamethasone; RRMM: Relapsed or Refractory Multiple Myeloma; NDMM: Newly Diagnosed Multiple Myeloma; CAR: Chimeric Antigen Receptor T cells; PET/CT: Positron Emission Tomography Computed Tomography; LDH: Lactate Dehydrogenase; SMM: Smoldering Multiple Myeloma

Introduction

Multiple myeloma (MM) is one of the most common hematologic disorders in US, which accounts for approximately 15% of hematologic malignancies [1]. The American Cancer Society estimates that more than 30,000 people will be diagnosed with multiple myeloma and nearly 13,000 will die of the disease this year [1]. The number of people diagnosed with MM has been increasing over the past ten years, fortunately, with the deeper understanding of the disease and advances in treatment and research, more novel therapeutic classes have been granted FDA approval and incorporated into treatment, which has significantly prolonged patients' survival [2]. To address recent discoveries about the molecular pathogenesis of the disease, International myeloma working group (IMWG) has redefined the basic diagnosis and response criteria [3,4]. Recently National Comprehensive Cancer Network (NCCN) has updated its guideline to reflect rapid progress in the management of multiple myeloma [5]. The purpose of this review is to highlight some of most recent changes and significant progress in multiple myeloma clinical practice from basic disease definitions to the advancement of therapeutic options.

Basic disease definitions and criteria

Revised diagnostic criteria: Historically, when the therapeutic options were limited and there was no apparent benefit from early treatment, multiple myeloma (MM) treatment would not be initiated if there was no sign of end-organ damage described in CRAB criteria. However, with emergence with novel agents and advanced technologies, the 5 year survival rate has been greatly improved and prevention of end-organ damage has become important [3]. To address this issue, the international myeloma Working Group (IMWG) updated definition of MM to include biomarkers in addition to existing requirements of CRAB features [4]. The diagnosis requires 10% or more clonal plasma cells on bone marrow examination or a biopsy proven plasmacytoma plus evidence of associated end-organ damage. Even if end-organ damage is not present, patients with ≥ 60% bone marrow plasmacytosis, involved: uninvolved serum free light-chain ratio ≥100 with the involved serum free light-chain ≥10 mg/dL, or more than 1 focal lesion on magnetic resonance imaging (MRI)

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studies are eligible for treatment [4]. The New IMWG diagnostic criteria not only allow for early therapy which could potentially improve survival, but also incorporate technology advances encouraging the use of modern imaging methods to make an early diagnosis. This new diagnostic criteria is included in the recently published National Comprehensive Cancer Network (NCCN) 2016 version of the Clinical Practice Guidelines in Oncology for Multiple Myeloma (MM) [5].

Updated response criteria: Based on Data from multiple clinical trials, the achievement of Complete Response (CR) has been shown to be a prognostic indicator of long-term progression-free survival (PFS) and Overall survival (OS) in patients treated by HDT/ASCT and novel agents, regardless of age, ISS stage and treatment [6]. Conventional Complete Response (CR), defined as disappearance of M-protein on immunofixation, on survival of MM has generated controversy in current literatures and in clinical practice. Improvements in techniques for assessing disease status have led to development of more stringent response criteria. As a result, IMWG further categorizes complete response into molecular CR, immunophenotypic CR and astringent CR [4]. With the new criteria, assessment of treatment response is transitioning from conventional CR to MRD negative status assessment and Stringent Complete Response in MM patients.

Minimal Residual Disease (MRD) refers to the persistence of small number of residual myeloma cells during or following treatment. Presence of MRD that is below the sensitivity of bone marrow (BM) morphology, protein electrophoresis with immunofixation and light chain quantitation will eventually lead to relapse, even in patient with CR [7]. Developments in new diagnostic techniques have allowed for the detection of minimal residual disease, which has emerged as one of the most relevant prognostic factors in both transplant candidates and elderly patients who are not considered to be transplant-eligible, irrespectively of patients' age and cytogenetic risk [8]. Response criteria studies have shown that among patients achieving a biochemical CR, MRD-negative status is associated with superior outcomes including progression-free survival (PFS) and OS [8-10]. In a multicenter randomized phase 3 trial, each log depletion of MRD was associated with significant improvement of OS (median OS of 1, 4, 5.9, 6.8 and >7.5 years for MRD ≥10%, < 10%, 0.1% to < 1%, 0.01% to < 0.1% and < 0.01% respectively) [8].

In order to sufficiently assess the deepness of response, more sensitive method should be utilized to measure and monitor MRD. Research shows that persistent MRD detected by multiparameter-flow-cytometry (MFC), polymerase-chain-reaction (PCR), Next-generation sequencing (NGS) indicates poor clinical outcome among patients with complete remission [11]. One recent study shows that using 2nd generation MFC, immune profiling concomitant to MRD monitoring also contributed to identify patients with different outcomes, being poor, intermediate and favorable outcome (25%, 61% and 100% OS at 3-years; P=.01) in the study) [7]. Newer imaging modalities including PET/CT and MRI scans have also been included in disease assessment and progression criteria [8].

Rawstron and colleagues report that a lower cutoff of 0.01% threshold (10−4) using more sensitive assays (e.g., next generation sequencing (NGS) or high-sensitive multiparameter flow cytometry (MFC)) will likely provide a better assessment of clinical outcome [8]. Martinez-Lopez's study further identified 3 groups of patients with different time to progression (TTP) using NGS: patients with high (<10−3), intermediate (10−3 to 10−5) and low (>10−5) MRD levels showed significantly different TTP (27, 48 and 80 months, respectively). According to this study, 10−5 could be considered as the target cutoff level for definition of MRD negativity [9]. MRD monitoring can be used to evaluate the efficacy of different treatment strategies and tailored therapy in MM. It is predictable that there will be increased reliance on minimal residual disease testing to guide therapy. Future efforts need to address systematic usage of highly sensitive, cost-effective and standardized MRD assessment techniques.

Cytogenetics and risk stratification: MM is characterized by significant tumor heterogeneity with clonal evolution affecting both prognostic stratification and therapeutic approaches. Genome instability represents an important feature observed in MM cells leading to emergence of genetic change which ultimately results in acquisition of drug resistance and disease progression [12]. Moreover, bone marrow microenvironment plays a role in supporting MM cell survival, proliferation and drug resistance [13]. Comprehensive oncogenomic analysis has identified many complex genetic and epigenetic alterations in multiple myeloma. A number of genetic aberrations such as t(4; 14) and 17p13 deletion have been shown to be associated with poor survival consistently across studies [14], whereas others are controversial with conflicting evidence in the literature. Although FISH-identified t(4;14), t(14;16) and del17p13 have been considered to convey poor prognosis [15], more recent single-nucleotide polymorphism array analysis in 192 uniformly treated patients identified amp(1q23.3), amp(5q31.3) and del(12p13.31) as the most powerful independent adverse prognostic markers (P< 0.0001) [15]. Even within groups with these genetic prognostic factors, there may be further heterogeneity. For example, the IFM group showed that among the patients with t(4; 14), those with a hemoglobin greater than 10 g/l and beta-2 microglobulin less than 4 mg/l had significantly longer survival compared to those without [15]. At the same time, a recent analysis showed that patients with high-risk genetic changes have significantly different survival depending on the presence or absence of trisomies [16]. Based on these findings, genetics alone should not be considered as prognostic factors. Combining information about genetic abnormalities with other parameters may improve their prognostic value. Future study could focus on clinical translation of acquired epigenetic knowledge such as genome instability and the exploitable vulnerabilities it creates, which could eventually lead to development of new treatment options [12].

The consensus statement on risk stratification released by the International Myeloma Working Group (IMWG) combined both disease burden and biology features for patients with multiple myeloma. The new IMWG risk stratification has three risk categories: low-risk, standard-risk and high-risk. A patient's risk classification is based on the disease stage according to the International Staging System (ISS), the presence of certain chromosomal abnormalities in the patient's myeloma cells based on results of FISH testing and patient's age [14]. Patients who are ISS stage II or III and whose myeloma cells contain the translocation t(4; 14) or the deletion

Table 1: International myeloma working group (IMWG) risk stratification.

	Criteria	Median OS	% Patients*
Low-Risk	ISS I/II plus absence of t(4;14),del17p,and+1q21 and age<55 years	>10 years	20%
Standard-Risk	Others	7 years	60%
High-Risk	ISS II/III plus t(4;14)or Del17p	2 years	20%

* % of patients with a give risk at diagnosis

Table 2: Revised international staging system (R-ISS).

R-ISS Stage	Criteria	5-Year OS	5-Year PFS	% Patents*
I	ISS I plus low LDH plus absence of t(4;14),t(14;16), or Del17p	82%	55%	28%
II	Not R-ISS I or III	62%	36%	62%
III	ISS III plus high LDH or t(4;14) or t(14;16)or Del17p	40%	24%	10%

*% of patients with a given disease stage at diagnosis

del(17p13) are classified as high-risk [14]. IMWG advocates use of ISS staging in conjunction with FISH for t(4; 14), deletion 17p13 and 1q21 gain for risk stratification in MM [14] (Table 1).

Risk stratification allows physicians to provide an expected survival time to inform a patient of his or her prognosis. Although we are not ready to recommend risk-adapted therapy yet, with more clinical research and understanding of the disease, ultimately, a patient's treatment can be tailored to their risk category with an aim to minimize side effects while maximizing the benefits of treatment. Risk stratification can also provide guidance for testing new therapeutic agents in clinical trials, i.e., more potent strategies can be tested for high risk patients who have poor outcome with current treatment strategies. Further studies should focus on further refining the risk groups based on the underlying biology of the myeloma cells.

Revised staging: Revised International Staging System (R-ISS) developed by the international Myeloma Working Group is included in The national Comprehensive Cancer Network (NCCN) 2016 version of the Clinical Practice Guidelines in Oncology for Multiple Myeloma (MM) [5]. In addition to the serum albumin and beta 2 micro globulin, serum lactate dehydrogenase and high-risk chromosomal abnormalities detected by interphase fluorescence in situ hybridization are also added to the staging system. Based on these risk prognostic features, patients were stratified into three subgroups with different survival outcomes [17] (Table 2). The revised staging system provides more prognostic information compared with the previous staging system. The previously widely used Durie-Salmon staging is no longer included in the 2016 NCCN guidelines [5].

The RISS was developed using data from patients enrolled in clinical trials. A recent study evaluated its role in unselected non-clinical trial patients with myeloma. A total of 381 patients were identified and retrospectively classified as having RISS I, II and III. RISS I exhibited a median overall survival and progression-free survival of not reached and 38.9 months compared with 77.9 and 26.9 months and 29.9 and 15.3 months for RISS II and III, respectively. Researchers concluded that these results correlated well with those seen in the International Staging System (ISS), confirmed the role of RISS in unselected nonclinical trial patients and suggest that increased serum lactate dehydrogenase (LDH)and high-risk cytogenetics are very robust prognosticators when combined with the ISS [18].

Redefining smoldering myeloma: More and more researchers are paying attention to the earlier, smoldering stage of the disease. The understanding of smoldering (asymptomatic) myeloma is evolving rapidly. Some studies have shown that patients with certain characteristics including IgG levels of > 3 g/dL, IgA of > 2 g/dL, or abnormal free light chain ratios [19] or urinary Bence Jones protein of > 1 g/24 [20] have an increased risk of progression to active (symptomatic) myeloma. The International Myeloma Working Group recently has included this category of patients into the diagnosis of multiple myeloma [4]. In 2016 NCCN guideline, the definition for Smoldering (Asymptomatic) Myeloma has been modified to include the following characteristics: IgG ≥ 3 g/dL; IgA > 1 g/dL or Bence-Jones protein >1 g/24h. With the new definition, patients could be treated before symptoms happen [5].

Korde and colleagues report that patients with cytogenetically high-risk smoldering multiple myeloma may benefit from early treatment with an effective regimen before end organ damage develops. Because these patients have a high probability (>90%) of disease progression within 2 years, there is a need to treat them with well-tolerated and effective regimens. In the group of 12 patients with high-risk but asymptomatic smoldering multiple myeloma, substantial disease eradication was observed, resulting in MRD negativity in all patients. By monitoring the MRD status during and after treatment, 12-month progression free survival was 100% in patients who became MRD negative by flow cytometry and next-generation sequencing. The above data confirm that with the introduction of highly effective drug combinations, traditional response criteria become less valid because these do not sufficiently assess the deepness of response. This study also encourages new ways of response evaluation such as MRD and PET/CT negativity to undergo clinical development and be eventually be integrated in clinical practice [10].

Recent treatment progress

Updated NCCN guideline with new treatment options: The *National Comprehensive Cancer Network (NCCN) recently* released an *updated* version of its *guidelines* for multiple myeloma. As initial management of myeloma, for both transplant eligible and non-transplant candidates, the triplet therapy of lenalidomide, bortezomib and dexamethasone is included as category 1 recommendation based upon phase III trial that shows its superiority over lenalidomide and dexamethasone [21]. The oral proteasome inhibitor ixazomib with lenalidomide and dexamethasone as an all oral initial regimen and cyclophosphamide, bortezomib and dexamethasone are now included as category 2A recommendation, based upon data from phase I/II clinical trials [22, 23].

In treatment of relapsed and refractory myeloma, some most recent progress are also reflected in 2016 NCCN guideline. Calfilzomib/dexamethasone combination is included due to its superiority over bortezomib/ dexamethasone in randomized trial endeavor [24]. Both oral proteasome inhibitor containing triplet (ixazomib/lenalidomide/dexamethasone) and monoclonal antibody containing combination (elotuzumab/ lenalidomide/dexamethasone) prolonged progression-free survival compared to lenalidomide/ dexamethasone in randomized trials [5,25,26]. Daratumumab is

included as Category 2A recommendation based upon single-agent activity in heavily treated patients with myeloma refractory to both bortezomib and lenalidomide in phase II clinical trials [5,27]. Combining panobinostat with bortezomib and dexamethasone has been included in the guideline basing upon panobinostat's activity in bortezomib-resistant myeloma in Panorama 2 [5,28].

Rapidly evolving novel therapeutics: Traditional chemotherapy and stem cell transplant have improved the survival of MM, but almost all patients eventually relapsed. With the deeper understanding of the disease, more novel therapeutic classes have been approved and incorporated into treatment. 2 years ago, a novel category of targeted drugs, the histone-deacetylase inhibitors, became available, with panobinostat being the first agent in this category. Last year, the U.S. FDA approved fours drugs for the treatment of multiple myeloma: panobinostat in combination with bortezomib and dexamethasone, single agent daratumumab, elotuzumab in combination with lenalidomide and dexamethsaone and ixazomib in combination with lenalidomide and dexamethasone. More drug classes undergoing clinical development include more monoclonal antibodies and agents with novel mechanism, such as a kinesin spindle protein inhibitor (filanesib) [3]. Alternative approaches, including vaccine therapy, Checkpoint inhibitors and chimeric antigen receptor (CAR) T cells, are also being explored for multiple myeloma in several ongoing clinical trials [29]. This review will highlight some recently approved and promising novel therapeutic agents with up-to-date clinical data.

Novel Proteasome Inhibitors: Next-generation proteasome inhibitor carfilzomib was first approved for multiple myeloma in 2012, as a single agent in patients who had received at least two prior therapies including bortezomib and an immunomodulatory agent. Then the US Food and Drug Administration (FDA) expanded the drug label for carfilzomib in combination with dexamethasone or with lenalidomide plus dexamethasone for patients with relapsed or refractory disease, based on results of the ENDEAVOR trial, which showed a median progression-free survival of 18.7 months in patients assigned carfilzomib compared with 9.4 months for patients assigned bortezomib (hazard ratio, 0.53 [95% CI, 0.44–0.65]; *P*< .0001) [24]. In Aspire trial, which compared carfilzomib combined with lenalidomid and dexamethasone (CRd)with lenalidomide plus dexamethasone in patients with relapsed multiple myeloma, progression-free survival with CRd was 26 months compared with 17 months in the control group with no difference between high-risk vs. standard-risk FISH subgroups. Along with other trials, Aspire demonstrates the benefit of adding the second-generation proteasome inhibitor carfilzomib to a standard two-drug salvage regimen of lenalidomide and dexamethasone with limited toxicity [30] and prepares the ground for use of carfilzomib combinations in the front-line treatment of multiple myeloma. Recently Korde and colleagues report and pilot study of CRd for 45 patients with newly diagnosed multiple myeloma (NDMM) with promising study results. In this trial, carfilzomib-containing combination is tolerable and demonstrates high rates of MRD negativity in NDMM, translating into longer progression-free survival in patients achieving MRD negativity. Carfilzomib-lenalidomide-dexamethasone therapy also demonstrates efficacy in high-risk smoldering multiple myeloma (SMM). More studies are warranted to test additional modifications such as subcutaneous administration and a weekly schedule of carfilzomib administration, which may further enhance the tolerability and acceptance of such combinations [10].

Ixazomib is the first orally administered therapy in the same family of proteasome inhibitors with bortezomib and carfilzomib. Ixazomib recently was approved by the FDA for the treatment of multiple myeloma based on the randomized Phase 3 TOURMALINE-MM1 study comparing the study arm (ixazomib/lenalidomide/dexamethasone) to the control arm (lenalidomide and dexamethasone) in patients who have received one to three prior treatments. Patients refractory to previous proteasome inhibitor-based or lenalidomide-based treatment were excluded from the study. After a median follow-up of almost 15 months, progression-free survival was superior in the study arm compared to the control arm (20.6 months versus 14.7 months, p=0.012). Overall response rates (78.3% vs 71.5%, p=0.035) and complete response rates (11.7% vs 6.6%, p=0.019) were also improved in the three-drug arm. Patients with high-risk cytogentics had a similar HR and PFS compared to the rest of study population. Grade 3 or greater adverse events such as neutropenia, anemia, thrombocytopenia and pneumonia were reported in 68% and 61% of patients in the group treated with ixazomib and the control group, respectively 2. Serious adverse events were reported in 40% and 44% of patients in the ixazomib and placebo groups, respectively [25].

Researchers are also been studying the role of ixazomib in newly diagnosed myeloma patients and have presented preliminary data at 2016 ASCO Annual Meeting. This is a Phase 1/2 trial of ixazomib, cyclophosphamide and dexamethasone for newly diagnosed multiple myeloma. The ixazomib containing combination is well tolerated with high response rates and offers the opportunity to utilize a completely oral regimen, which also is less expensive and more convenient to take compared with the lenalidomide combinations. Future studies should assess its efficacy against other proteasome inhibitor combinations [31].

Histone deacetylase inhibitor: Panobinostat is a pan-deacetylase inhibitor that exhibits anti-myeloma activity through epigenetic modulation of gene expression and inhibition of protein metabolism of class I and II histone deactylase (HDAC) enzymes [32]. It is approved by FDA for treatment of multiple myeloma for the use in combination with bortezomib and dexamethasone for patients with relapsed/refractory MM who have had at least 2 prior therapies with regimens containing an immunomodulatory agent and bortezomib. The approval was based on the results of progression-free survival (PFS) in a subgroup of 193 patients from the randomized, two-arm, placebo-controlled phase III PANORAMA-1 study. The median PFS values were 10.6 and 5.8 months in the panobinostat arm and control arm, respectively [HR 0.52 (95% CI: 0.36, 0.76)]. Overall response rates were 58.5% (95% CI: 47.9, 68.6) in the panobinostat arm and 41.4% (95% CI: 31.6, 51.8) in the placebo arm [33]. Safety data from 768 patients enrolled in PANORAMA-1 study shows that most common adverse reactions (>20%) on the panobinostat-containing arm were diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia and vomiting. Serious adverse reactions included pneumonia, diarrhea, thrombocytopenia, fatigue and sepsis. ECG changes occurred in 64% of patients in the panobinostat-containing arm and 42% in the control arm. Arrhythmias occurred more frequently in patients receiving panobinostat compared to the

control arm (12% vs. 5%). As a result, panobinostat is approved with a Boxed Warning for fatal cardiac toxicities and severe diarrhea [33].

The PANORAMA-2 is a phase II single arm, multicenter trial that evaluated combination of panobinostat with bortezomib and dexamethasone in patients who had relapsed disease that was refractory to bortezomib (N=55) [28]. Patients on this study achieved an ORR of 34.5% with the panobinostat-containing regimen [28]. The median PFS was 5.4 months and OS had not been reached at a median follow-up of 8.3 months [28]. Common grade 3/4 adverse events included thrombocytopenia (63.6%), fatigue (20%) and diarrhea (20%) [28]. Given that in the clinical trials panobinostat frequently causes severe diarrhea especially in combination with bortezomib, further studies could evaluate combing panobinostat with different agents, especially those with less additive GI side effects.

Immunotherapies

As the newest therapeutic approach to multiple myeloma, immunotherapies are emerging as a promising treatment option for this currently incurable disease. Innovative approaches such as B-cell specific monoclonal antibodies, CAR T cells and checkpoint inhibitors utilize the immune system to stimulate a "host-vs-myeloma" effect and then target and eradicate malignant cells [34].

Monoclonal antibodies: Daratumumab is a human IgG Kappa monoclonal antibody that targets the CD38 surface protein on myeloma cells, which induce apoptosis and modulation of CD38 enzymatic activity, *Complement Dependent Cytotoxicity* (CDC), Antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis. Daratumumab is the first monoclonal antibody approved for use as monotherapy in multiple myeloma patients who have received at least three prior lines of therapy based on two single-arm trials. In the first trial, 29 percent of patients experienced a complete or partial reduction in their tumor burden that lasted for a median of 7.4 months. In the second trial, 36 percent of patients had a complete or partial reduction in tumor burden. In these two trials, daratumumab showed single agent activity in the treatment of MM [35]. Grade 1/2 Infusion related reactions occurred in almost half of the patients, mainly during the first infusion. Although no study patients were discontinued due the infusion related reaction, prevention and management is crucial to avoid unnecessary treatment discontinuation [36].

Studies have also been conducted to investigate the efficacy of daratumumab in combination with other agents. At the American Society of Clinical Oncology (ASCO) 2016 Annual meeting, Dr. Antonio Palumbo presented initial findings from the pivotal phase 3 Castor trial of nearly 500 patients with relapsed or refractory multiple myeloma (RRMM)who were randomized to receive a three drug regimen that includes daratummab, bortezomib and dexamethasone or a two-drug regimen of bortezomib plus dexamethasone. Patients received eight cycles of either regimen, followed by daratumumab maintenance therapy. With median follow-up of 7.4 months, the daratumumab combination significantly improved median PFS (61% reduction in risk of progression) and doubled both very good partial response rates from 29% to 59% and complete response rates from 9% to 19% without significant additive toxicities. These results show that combination therapy with daratumumab may play a very important role in clinical practice. Future research is needed for longer patient follow up to determine the impact of this daratumumab combination on patient survival. As the CASTOR study shows that daratumumab can be combined with bortezomib and dexamethasone [37], other clinical trials are ongoing for combination of daratumumab with another standard therapy for recurrent multiple myeloma and the role of various daratumumab-based regimens for patients with newly diagnosed multiple myeloma.

Followed daratumumab, elotuzumab was granted approval by FDA for treatment of multiple myeloma. Elotuzumab is a humanized monoclonal antibody that exerts its anti-myeloma activity mainly through ADCC mediated by NK cells but no CDC [38]. This antibody binds to a different target-signaling lymphocytic activation molecule F7 (SLAMF7), also known as cell surface glycoprotein CD subset 1(CS1)-which is expressed on myeloma cells. Its approval was based on results of the ELOQUENT-2 trial, a Phase 3 randomized open label study of elotuzumab in combination with lenalidomide and dexamethasone (ERd) in 646 patients with relapsed refractory multiple myeloma. 32 percent of patients had a 17p deletion and 9 percent had a t(4;14)translocation, which are considered high risk chromosomal abnormalities. Although elotuzumab has no single agent activity in advanced MM, the results show that adding elotuzumab to lenalidomide and dexamethasone increase treatment response rates and prolongs progression-free survival due to a synergism [26].

Given the heavily pretreated population, the results for daratumumab and elotuzumab were very encouraging. With limited toxicity profile, they allow favorable combination therapeutics with existing as well as emerging therapies. Future study efforts could include incorporation of immunotherapy such as daratumumab or elotuzumab into frontline therapy or earlier phase of this disease.

CAR T cells in MM: *CARs are chimeric antigen receptors, or proteins that allow the T cells to recognize a specific protein on tumor cells, which then leads the immune cells to attack the cancerous cells.* Chimeric antigen receptor (CAR) T cells are immune cells genetically modified to recognize and eradicate cancer cells that have specific target proteins on their surface. Chimeric antigen receptor (CAR) T cell therapy has proven to be an exciting approach in treating leukemia. Recent study shows that CAR-T cell therapy is also very promising in management of MM [39].

At the ASCO 2015 meeting, Dr. Alfred L. Garfall reported the very first trial of CAR T cells in myeloma. This trial utilized CD19-targeted CAR T cells and enrolled patients who had relapsed within one year of a prior autologous stem cell transplant. Patients received CAR T-cells following a second autologous stem cell transplant. Three out of five patients remained in remission with follow up ranging from 74 days to 339 days. CD-19 is infrequently expressed on MM cells and is not generally considered a strong target. However, there is a subpopulation of MM clones with drug-resistant, disease-propagating properties that have CD-19-positive B cell phenotype [40]. In his case report published in the New England Journal of Medicine, outcome of autologous transplant followed by treatment with CTL019 cells (autologous T cells expressing a CD3-zeta/CD137-based ant-CD-19 CAR form a lentiviral vector) were reported. One year after treatment of a patient, who has received nine prior lines of therapy, study results demonstrated a complete response with

no evidence of disease progress and no evidence of monoclonal immunoglobulin on serum and urine immunofixation [39].

Preliminary data of a phase I trial of CAR T-cell therapy targeting the anti-B cell maturation antigen (BCMA) was presented at the 2015 American Society of Hematology (ASH) 57th Annual meeting &Exposition. B-cell maturation antigen (BCMA or CD269), is also known as tumor necrosis factor receptor super family member 17 (TNFRSF17), which is expressed on nearly all multiple myeloma tumor cells, while it is restricted to plasma cells and a subset of mature B cells in term of normal tissue expression. Patient T cells were harvested and genetically modified to produce the BCMA-targeted CAR T cells. Each patient received a single infusion of their modified T cells after first being administered a chemotherapy regimen of cyclophosphamide 300 mg/m^2 and fludarabine 30 mg/m^2 for three days to enhance activity of the CAR T cells by deleting endogenous leukocytes. This was a small study involving very heavily pretreated patients with advanced multiple myeloma. Among a total of twelve patients, two patients were treated at highest dose level reached one very good partial response and one stringent complete response respectively. Patients with the best response to the CAR-B cell maturation antigen therapy also experienced the most toxicities including cytokine release syndrome, neutropenia and low platelet counts [41].

As CAR T-cell therapy is demonstrating clinical efficacy in hematological malignancies, they also have the capacity to elicit expected and unexpected toxicities. Recently, several cases of severe neurotoxicity related to CAR-T cells use have been reported in leukemia patients. Cytokine-release syndrome (CRS) is another serious side effect associated with CAR T-cell therapy, which is the result of T-cell activation and its presence actually indicates a positive response to therapy. Some patients may experience high fevers, low blood pressure, delirium and seizure typically occurring within the first week of treatment. Tocilizumab, a humanized monoclonal antibody directed against interleukin-6 receptor, has been used to manage CRS. Along with optimal supportive care strategies, CAR T cells may become better tolerated over time [42]. CAR T cell approach has emerged as a very promising immunotherapy, however it is still in early stage. More clinical trials are needed to evaluate its efficacy and safety in the treatment of multiple myeloma. The challenges clinicians facing are to balance efficacy and toxicity during CAR T cells management.

Checkpoint inhibitors: Checkpoint proteins, such as PD-1 (programmed cell death protein-1) on T cells and its ligands (PD-L1, PD-L2) on tumor cells allow the immune system cells to be turned on and off as needed. The binding of PD-L1 to PD-1 transmits inhibitory signal to inactivate T cells preventing them from eradicating the cancer cells. As a result, the PD-1 pathway is often utilized by tumors to escape from immune surveillance. Blocking the binding of PD-L1 to PD-1with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1 monoclonal antibodies) takes the brakes off the immune system and allows the T cells to eliminate tumor cells. Anti-PD-1 / PD-l1 agents have a good safety profile and have resulted in duration responses in a variety of cancer [43].

The successful use of checkpoint inhibitor in other types of cancer has stimulated the interest in expanding its role in MM. First, researchers reported that treatment with single-agent PD-1 inhibitor nivolumab led to stable disease as the best response in patients with relapsed/refractory multiple myeloma. And then, pembrolizumab, another inhibitor of PD-1, approved for advanced melanoma and non–small cell lung cancer, has demonstrated more robust antitumor activity when combined with immune-modulatory drugs [43]. In a phase II study of 33 patients, pembrolizumab was combined with lenalidomide/dexamethasone in phase I study of 50 patients (KEYNOTE-023) and with pomalidomide/dexamethasone. Of notes, all patients were heavily pretreated. The response rate was 76% to pembrolizuman in combination with lenalidomide and dexamethasone and 60% to pembrolizumab plus pomalidomide and dexamethasone [43,44]. Adverse events were consistent with previous studies of pembrolizumab in other cancers. Although the data are encouraging they are still preliminary, more clinical studies are needed to further define the role of pembrolizumab in MM [43,44].

Other promising agents on the horizon: Several promising novel agents have been extensively developed and tested in clinical trials. Selinexor is a first-in class SINE XPO1 antagonist being evaluated in various combinations in heavily pretreated patients [45]. A novel, highly potent proteasome inhibitor marizomib, which irreversibly binds and inhibits all 3 proteasome subunits, is being studied as monotherapy as well as in combination with pomalidomide and dexamethasone [46]. Vorinostat, the first FDA approved histone deacetylase (HDAC) inhibitor for treatment of patients with cutaneous T cell lymphoma (CTCL), is also being evaluated in various combinations for relapse/refractory myeloma [47-49]. Dinaciclib, a small-molecule inhibitor of cyclin-dependent kinases 1, 2, 5 and 9, demonstrates singe-agent activity in relapsed multiple myeloma [50]. A new study has shown that when combined with the PARP1/2 inhibitor ABT-888, dinaciclib disrupted homologous recombination function and sensitized myeloma cells to PARP inhibition resulting in multiple myeloma cell death [51]. Plitidepsin, an investigational marine-derived anticancer agent, oprozomib, an oral proteasome inhibitor, filanesib, a kinesin spindle protein inhibitor, a potent and selective BCL-2 inhibitor ABT-199, a Pan PIM kinase inhibitor LGH447 and BET bromodomain inhibitors targeting oncogene Myc, such as GSK525762 and CPI-0610 are also under clinical development.

Conclusion

Although Multiple myeloma is a highly complex and heterogenous disease, new treatment options have gradually improved survival rate for multiple Myeloma patients and led to a substantial change during the last decade. There is no doubt that there will be further improvement in survival rates, as well as a deeper understanding of disease biology, particularly of the way myeloma cells interact with their microenvironment. With many potential treatment strategies available, choosing among treatments and making the right decision on treatment sequence sometime could be difficult and challenging. In addition to learning about the efficacy, understanding the toxicities with those novel therapeutic agents is also essential to understanding how to use the new regimens in practice. One key question in practice is how to better treat relapsed myeloma with new combinations of therapies that are more effective in fighting multiple myeloma, i.e., the use of immunotherapy drugs with chemotherapy, which is in the early stages of research but is already showing a lot of potential. Many

promising clinical studies are ongoing and will provide additional insight into the optimal use of these medications in combinations with other conventional and novel agents, in which they may synergize and provide a greater impact in disease course. Better endpoints than progression free survival (PFS) are also needed in the clinical trials to incorporate patient experience and better predict clinical benefit of regimen. Despite that there has been a debate of whether autologous stem cell transplantation (ASCT) is needed in the era of novel targeted agents, high-dose chemotherapy and autologous stem cell transplantation (ASCT) improve the depth of remission translating into better PFS and OS and still remain standard of care especially for younger, fit patients with multiple myeloma. However, the timing of transplantation and role of maintenance need to be further evaluated and discussed. Moreover, continuous efforts are needed to enable new response criteria development and new biomarkers discovery to help clinicians to identify more at risk patients and guide clinical practice. Ultimately, we are going to individualize treatment or tailor treatment depending on major risk factors from genetic to molecular level, patient preference, prior side effects and convenience of administration. With the emergence of the new therapies and more understanding of the genetics of multiple myeloma and the potential association to patient outcome, we are running to a new era where advances in cancer research and novel treatments may eventually pave the way for multiple myeloma treatment from coping to cures.

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