Multiple Myeloma: Treatment is Getting Individualized

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Abstract Multiple myeloma (MM) is a heterogeneous disease with varied outcome. The novel agents including two major classes of drugs; the immunomodulatory drugs and the proteasome inhibitors with unprecedented response rates, have replaced conventional chemotherapy. With monoclonal antibodies on the horizon, outcome of this disorder will further improve. Progression in risk stratification systems has made it possible to predict the disease course as well as outcome in myeloma patients with disease categorization into low to high risk. In addition, detection of minimal residual disease by serum free light chain assay, flow cytometry, molecular techniques like polymerase chain reaction and positron emission tomography scan is playing an important role in modifying the treatment. An extensive research in the disease biology has improved our knowledge regarding interplay between myeloma cells and elements of the bone marrow microenvironment which contribute to sustain proliferation and survival as well as de novo drug resistance. Again, insight into the role of genetic and epigenetic interactions in MM has exposed new molecular targets. All these have opened the gateway for novel therapeutic strategies with focus on risk based individualized therapy.

Keywords Myeloma · Personalized · Treatment · Risk · Stratification · Novel

Disease at a Glance

Multiple myeloma (MM) is one of the plasma cell dyscrasias characterized by clonal proliferation in the bone marrow and presence of monoclonal protein in the blood or urine or both. The disease spectrum ranges from asymptomatic monoclonal gammopathy of unknown significance to the dreaded variety of plasma cell leukemia. Hypercalcemia, renal impairment, anemia and bony lesions represent the CRAB criteria for symptomatic MM requiring therapy. Improved understanding of disease pathology has resulted in development of more effective therapies [1, 2]. At the backdrop of this, risk adapted approach is being discussed explicitly in scientific forums and consensus guidelines are led to obtain more effective disease control [2]. The therapy for individual patient is unique and is based on a number of factors, including, age and general health, results of laboratory and cytogenetic tests, symptoms and disease complications, prior myeloma treatment, patient's lifestyle, goals, views on quality of life and personal preferences. There are approximately 19,000 new cases/year in United States and an Indian incidence of MM is 6000 new cases/year. The male to female ratio is 1.4:1 and mean 5-year survival rate is 33 % [3, 4]. Median age of diagnosis in western world is 70 years while the same in India is 60 years [5]. The initial treatment for a myeloma patient depends upon eligibility for high-dose chemotherapy (HDT) and autologous hematopoietic stem-cell transplantation (ASCT) which in turn is based upon various factors such as age, performance status and co-morbidities. Patients who are <65 years of age with no major co-morbid conditions are candidate for induction therapy of 4–6 months followed by ASCT [3, 6]. A combination of immunomodulators (IMiDs) (thalidomide or lenalidomide) or proteasome

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inhibitors (PI) (bortezomib) with dexamethasone is used for induction. The response rate with these novel agents (overall response rate: complete and partial rate of 60–90 %) is superior to that of conventional therapy [vincristine, adriamycin and oral dexamethasone pulse (VAD); vincristine, adriamycin and methyl prednisolone (VAMP)] [7, 8].

Risk Stratification

MM is a biologically complex disease, with great heterogeneity in genetic aberrations as well as overall response and survival of patients. There is extreme diversity of clinical manifestations of MM with patients ranging from more aggressive disease characterized by disease resistance and fatal outcome to patients who have relatively indolent disease requiring intermittent therapy and associated with lengthy survival. The aim of any risk stratification system is adding factors to assign the risk to each patient and further allowing the better optimization of therapeutic resources to improve depth and duration of response.

The Durie–Salmon Staging System (DSS) [9] and the International Staging System (ISS) [10] are the two most commonly used risk stratification models. Both the systems based on tumor burden, though have significant clinical utility, are not devoid of limitations. DSS is almost redundant today considering low specificity of its factors (e.g. hemoglobin and S. creatinine), use of older techniques such as radiological skeletal survey [being replaced by superior imaging techniques like magnetic resonance imaging (MRI) and positron emission tomography (PET)/computed tomography (CT scan)] and less predictability (use of novel agents with better efficacy lead to tumor reduction). ISS, though, convenient to use, requires addition of cytogenetics/fluorescence in situ hybridization (FISH) to make it more robust in current era of novel therapies [11]. By conventional techniques, cytogenetic abnormalities are detected in only 30–40 % of patients; this gross underestimation is result of low mitotic index of malignant plasma cells, the telomeric locations of some of the chromosomal changes and the variable degree of bone marrow infiltration [12, 13]. FISH, with its ability to detect changes in interphase cells, can overcome the problem of lack of proliferating cells and can be informative in almost all myeloma patients [14]. International Myeloma Working Group (IWMG) consensus has recommended combination of ISS (serum Beta-2 microglobulin and serum albumin) and FISH [t(4;14), 17p13 and 1q21] for risk stratification of MM patients [15]. Additionally, testing for chromosome 1 abnormalities is also strongly recommended by the European Myeloma Network. An extended panel, which may be incorporated in clinical trials, thus includes testing for

t(11;14), t(14;20), del(13q) and ploidy status. [16]. More recent techniques such as high density comparative genomic hybridization, single-nucleotide polymorphism arrays and gene expression profile (GEP) show genomic aberrations in all MM patients [17]. GEP is speculated as a novel prognostic tool to further improve risk stratification with identification of subclasses of hyperdiploid MM with different clinical outcomes [18]. Comprehensive study using microarray technology by Jianxiang Chi et al. has demonstrated association of microRNAs with diagnosis, pathogenesis and prognosis of MM, thus representing it as a novel biomarker [19]. Other factors including serum lactate dehydrogenase, IgA, extramedullary disease, renal failure, high serum free light chain/serum-free kappa by serum-free lambda ratio, plasmablastic disease and plasma cell leukemia do not indicate high risk when considered in isolation, but collectively these features often determine high risk [11].

Novel Agents

There is a paradigm shift in the disease management of MM considering introduction of novel agents and ASCT as well as improvements in ancillary therapies. We have moved from use of melphalan and prednisone combination with median survival of 2–3 years to high dose chemotherapy followed by ASCT with a median survival of 4–5 years. Two new classes of molecules, namely IMiDs (e.g. thalidomide, lenalidomide) and PI (e.g. bortezomib) which are instrumental in improving the prospects of myeloma patients are associated with median survival of more than 7 years [20]. Bortezomib resistance further prompted research in this field and this led to introduction of second generation PI (e.g. Carfilzomib, Marizomib and MLN 9708), deubiquitylating enzyme inhibitors (e.g. P5091) and inhibitors of aggresome pathway (e.g. Vorinostat or Panobinostat) [21]. Last decade has also witnessed various synergistic combination therapies being explored such as pegylated doxorubicin with bortezomib [22], immunomodulatory drugs with corticosteroid [23, 24]. Other class of drugs, targeting immune dysfunction such as monoclonal antibody based therapies are also gaining popularity with Elotuzumab showing good response rate in relapsed MM when combined with lenalidomide [25].

Minimal Residual Disease

With the advent of novel therapeutic strategies, more myeloma patients are achieving complete response to treatment with improvements in both progression-free

survival and overall survival [26]. Therefore, in addition to pre-therapeutic factors, post-therapy response status has also emerged as an important prognostic marker [13]. The definition of complete remission (CR) has evolved over time. IMWG has defined CR as absence of detectable serum and urine monoclonal proteins by immunofixation as well as an undetectable plasma cell population within the BM. Additionally, stringent CR (sCR) [27] includes these parameters along with a normal kappa: lambda free light chain ratio. However, the present definition of sCR represents a threshold to the limit of detection indicating the necessity of development of reproducible sensitive assays to detect minimal residual disease (MRD). These include allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and immunophenotypic assays by use of more than seven-color multiparameter flow cytometry (MPF) with detection potential of one clonal cell in 10^5 normal cells and 10^4 normal cells respectively. ASO-PCR, though cumbersome, was more sensitive than MPF, with both assays being more sensitive in defining prognosis [28]. However, most patients who have achieved MRD negative status eventually show relapse highlighting the need to have a more sensitive and specific method. The utility of high-throughput sequencing based MRD detection has shown to meet this expectation with good degree of concordance between MPF (concordance rate of 83 %) and ASO-PCR (concordance rate of 85 %) with sequencing [29]. Bone marrow MRI [30] and PET [31] have also been demonstrated to be effective techniques by detecting focal lesions in BM. However, the prognostic implications of detecting MRD by these techniques in management of MM patients and further to conform tailor made therapy needs to be studied in future studies.

Era of Personalized Therapy

Despite the improvement in MM treatment, MM still progresses into a drug resistant phase and remains incurable. With the wealth of knowledge regarding genetic and molecular changes underlying the myeloma pathophysiology, many molecular targeted therapies including cell signaling targeted therapies are in development for the treatment of relapsed/refractory MM [32]. The genomic abnormalities and their individualized therapy are described in Table 1. Additionally, role of epigenetic aberrations such as DNA methylation, histone modifications and non-coding RNA expression in MM pathogenesis have steered the myeloma management in new direction with discovery of promising targets [33]. Amongst these novel targeted therapies, inhibitors of histone deacetylase (HDAC) [34, 35], Aurora kinase [36], PI3K/AKT/mTOR pathway [37, 38], heat shock protein 90 [39, 40], B cell activating factor

[41, 42] and cyclin dependent kinase [43] are being studied with combination of bortezomib to assess their effectiveness in bortezomib resistance. With the continued rapid evolution in disease biology, it is discovered that BM extracellular matrix, cytokines, chemokines and growth factors forming BM milieu play a crucial role in growth, survival, adhesion, migration and apoptotic resistance of MM cells [44]. The therapies targeting tumor microenvironment such as hypoxia, angiogenesis, integrins, CD44, C-X-C chemokine receptor type 4, and selectins are thus being explored in studies [32]. With this deluge of treatment choices, it is a challenge to select the best treatment option for a patient. Therefore, a better therapeutic strategy would be to use synergistic combinations of novel drugs aiming to reduce the drug resistance with more potent less toxic personalized therapies. With focus on personalized therapy, mSMART guidelines have stratified MM patients into three groups to make the most of new drug therapy: high risk, intermediate risk and low risk [2]. Treatment of high risk patients focuses on combining various aggressive modalities including multi-agent (3 or 4-drug) induction chemotherapy, HDT/ASCT or even auto-allo tandem SCT, further consolidation and aggressive maintenance using 2-drugs including bortezomib [13, 45]. Additionally, upfront use of newer proteasome inhibitors (Carfilzomib and others) [46], second generation IMiDs (Pomalidomide) [47] and monoclonal antibodies (Daratumumab and Elotuzumab) may be useful [48]. In contrast, low risk patients with a better life expectancy are suitable for less toxic sequential therapy approach although there is a fear of under treatment and inferior outcomes [24]. The individualization of therapy does not end with initial induction and consolidation but has to be incorporated into therapy of relapsed patients as well. Again, use of these novel agents alone may not confer the required treatment goal due to heterogeneity in tumor clones. Recurrent mutations can occur even late in the evolution of a tumor thus necessitating combination of molecularly targeted therapies with current approved treatment strategies [13, 49]. The important considerations of individualized therapy are provided in Table 2.

Future of Personalized Therapy

The future of myeloma therapy should thus aim at integrated approach in selecting the treatment strategy taking into account patient's clinical status, biochemical factors and targeting the genetic and/or epigenetic abnormalities present in individual MM tumor [13]. Thus, for MM induction, combination of conventional novel agents such as PIs and/or IMiDs and steroid with additional agents based on patient specific genomic abnormalities such as

Table 1 Genomic abnormalities and individualized therapy

Genomic event	Incidence (%) [12]	Target/gene	Risk/prognosis	Potential drug class/treatment strategy
del(13q)	50	Deletion of 13q	Intermediate risk (by cytogenetics) The negative prognostic impact is mainly related to its frequent association with del(17p) and t(4;14)	The adverse impact of del(13q) can be overcome with use of bortezomib + lenalidomide + dexamethasone [52] and/or allogeneic SCT [53]
Hyperdiploidy: more common in elderly patients and high incidence of bone disease. [54]	50	Trisomies of the odd numbered chromosomes 3, 5, 7, 9, 11, 15, 19, and 21	Standard risk generally favorable, but when associated with adverse cytogenetics shows poor prognosis	Sequential therapy approach [55]
t(4;14)	15	Dysregulation of FGFR3 and MMSET	Intermediate risk by FISH but high risk in absence of use of bortezomib based induction, consolidation and maintenance (12)	FGFR inhibitor: dovitinib [56]; MMSET: histone methyltransferase inhibitors [50] Use of up-front auto-allo tandem SCT [45]
t(11;14)	15	Upregulation of cyclinD1	Standard risk (by FISH) Variable prognosis: some studies showed favorable, some showed no impact	CDK inhibitors: seliciclib, dinaciclib
t(14;16)	5	Dysregulation of MAF	High risk	MEK inhibitor: selumetinib [57]
t(14;20)	1	Dysregulation of MAFB	High risk	GSK3 inhibition could be a new therapeutic target. Also, low efficacy of bortezomib in these class [58]
del(17p)	10	Deletion of 17p; p53 [59]	High risk	Aggressive treatment with 3-drug combination (triplet) of which one has to be bortezomib, HDT/ASCT, aggressive maintenance with 2 drugs and probably allogeneic SCT early in the treatment [45]
amp(1q21)	30–43 40 % of all newly diagnosed cases of MM and in about 70 % of cases of relapse [60]	Over expression of cell cycle-related gene <i>CKS1B</i> is predictor of poor survival [61]	Poor prognosis; depends upon copies of genes, >3 copies have worst prognosis	Bortezomib based therapy can improve progression free survival. This could be attributed to the close relations between Amp (1q21) and high-risk cytogenetic abnormalities, such as t (4; 14) [62]

ASCT hematopoietic stem cell transplantation, *CDK* cyclin dependent kinase, *CKS1B* cyclin-dependent kinases regulatory subunit 1B, *FGFR3* fibroblast growth factor receptor 3, *FISH* fluorescence in situ hybridization, *GSK-3* glycogen synthase kinase-3; *HDT* high dose therapy, *MAF* musculoaponeurotic fibrosarcoma, *MAFB* musculoaponeurotic fibrosarcoma oncogene homolog B, *MEK* mitogen-activated protein kinase (MAPK)/extracellular-signal-regulated kinase (ERK) kinase, *MMSET* multiple myeloma SET domain, *SCT* stem cell transplantation

activated Ras/Raf pathway, p53 abnormality, multiple myeloma SET domain (MMSET) or specific HDAC upregulation [50]. Then, lenalidomide or newer agents under investigation, can be used as maintenance therapy [21]. Recently, miRNA therapeutics, using either miRNA inhibition or miRNA replacement approaches, have been projected as a new exciting approach in MM treatment with potential advantage of late resistance in the therapy [51]. In addition to better risk stratification, the focus

could be on development of predictive biomarkers which are useful for individualizing treatment as only few such as cereblon expression (predictive of IMiDs) and expression of certain genes such as TRAF3 deletion or mutation (predictive of bortezomib) exist currently [15]. The personalized approach targeting deregulated pathways of a specific tumor, though still in infancy, represents a path by which we can hope to achieve long term disease control.

Table 2 Important considerations in Individualized therapy

Risk factors	Important considerations
Age over 75 years [63]	(1) Minimize toxicity with appropriate dose adjustments or use of modified treatment regimens
Frailty [63]	(2) Generally, ineligible for autologous stem cell transplantation (3) Dose reduction of melphelan and steroid (4) Use of novel agents such as proteasome inhibitors and immunomodulators
Comorbidities	
Cardiac [13]	(1) Use of corticosteroids with caution
Renal [64]	(1) Bortezomib is the drug of choice in patients with renal impairment (creatinine clearance <60 ml/min) (2) Dialysis may reduce the concentration of bortezomib, and it should be administered after dialysis
Neuropathy [38]	(1) Preclude use of bortezomib and probably thalidomide (2) If required, bortezomib in attenuated doses and by subcutaneous route using once weekly schedule
Bone disease [13]	(1) Prolonged use of bisphosphonates and preferably Bortezomib based therapy

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Compliance with Ethical Standards

Conflict of Interest The author did not receive financial compensation for authoring the manuscript.

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