Consensus in the Management of Multiple Myeloma in India at Myeloma State of the Art 2016 Conference

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REVIEW ARTICLE

Consensus in the Management of Multiple Myeloma in India at Myeloma State of the Art 2016 Conference

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Abstract The science of multiple myeloma (MM) and related plasma cell disorders is rapidly evolving with increased understanding of the disease biology and recent approval of the newer drugs widening the therapeutic armamentarium. Despite multiple international guidelines regarding the management of this disease, the practice of managing MM is not uniform amongst Indian physicians. There are challenges in management which are unique to the Indian patients. This review discusses these challenges and the consensus of the nation-wide experts in dealing with the same. We also briefly highlighted the perspective of international experts as discussed in the Myeloma State of the Art conference held in September 2016 at PGI, Chandigarh. An **I**ndian **M**yeloma **A**cademic **G**roup**e** (IMAGe) group was formed to strengthen the research, create awareness about myeloma and related disorders and form consensus guidelines/ recommendations that can be adapted to the Indian Scenario.

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Introduction

The understanding of disease biology and therapeutics of Multiple Myeloma (MM) is rapidly evolving. In our country, MM is managed by clinical hematologists, medical oncologists, radiation oncologists, nephrologists, orthopedicians as well as general physicians. Despite multiple international guidelines regarding the management of this disease, the practice of managing MM is not uniform amongst Indian physicians. There are challenges in management which are unique to the Indian MM patients. These challenges result from a multitude of factors including differences in disease biology (late presentation), constraints in the availability of various diagnostic and therapeutic armamentaria in our country, patient tolerance to therapy, and acceptability and affordability for the same. In an attempt to discuss these challenges and establish uniformity in managing MM patients, Myeloma Sate of the Art 2016 conference was organized from 30th September to 1st October 2016 at PGIMER Chandigarh. A total of 57 centers from India and abroad including 77 faculty members, 380 delegates including 52 DM/DNB residents participated in the conference.

Regional Challenges

There are multiple region-specific issues in India for rendering myeloma care such as (a) treatment-related constraints in the form of availability of hematopoietic stem cell transplant (HSCT) and the reluctance to avail HSCT, both by the

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physicians and the patients. (b) Patient-related issues, such as frequent change of doctors/health care facilities and the compliance. (c) Institution related issues such as individual institutions working in isolation without data sharing and finally, (d) financial constraints. Health insurance coverage in India is 5.51% (vs. 83.3% of Americans being insured) [1].

Consensus on MGUS

1. *Screening for MGUS in India* The epidemiological data on MGUS from India is not available. The data from the US suggests that it is present in 3% of the population above 50 years of age and 5% population above 70 years of age [2]. It is now well established that all MM patients evolve from MGUS and hence it is important to diagnose MGUS. The median age of MM patients in India is almost one decade younger than the western population [3]. Hence it was a consensus among participants that it is important to do epidemiological studies in India and study the risk factors for MGUS. Current recommendations, however, do not support screening for MGUS either for individuals or on a population basis [4].
2. *Investigations in a patient with MGUS* A complete blood count with ESR, liver and renal function tests should be done in all of these patients. Further, quantification of M band, serum immunofixation, and serum free light chain should be performed for further risk stratification of MGUS. It is also important to rule out primary amyloidosis by history, clinical examination and investigations like 24 h urinary proteins. Consensus could not be achieved on performing bone marrow (BM) examination. It was felt that a routine BM is not required if the clinical evaluation shows that is a low-risk MGUS (M-band less than 1.5 gm/dl, the absence of end-organ damage and IgG type) [5]. However, patients coming to institutes may undergo BM examination as part of their routine protocol or in a research setting.
3. *Radiological investigations (Skeletal survey, MRI, PET-CT)* Skeletal survey should be done in all patients as it is cheaper and available in almost all centres. MRI has limited benefit. PET-CT of the whole body can be avoided in patients with MGUS unless there is a strong suspicion of oligo-secretory MM or patient has a high risk of progression. The role of low dose whole body CT needs to be explored, as it is not available in most centres in India.

Consensus on Work Up of Newly Diagnosed MM and Disease Monitoring

The constraints to investigating a patient of MM in the Indian setting include the availability of laboratory infrastructure in the form of equipment, expertise, and quality assurance, financial affordability of patient and travel to health facility etc. Hence wherever possible, the treating physician should strive to follow the following consensus recommendations

1. *Plasma cell percentage* There is a huge variability in the plasma cell percentage being reported between pathologists, and even in the same patient—between different slides. Ideally, we should have 1000 cell mononuclear cell count for correct estimation of the plasma cell percentage, which is rarely done in most Indian laboratories owing to the workload and the scarcity of the qualified pathologists. Also, the IHC on BM biopsy and aspirate is not widely available, even in areas where it is available, the pathologists don't routinely report clonal plasma cell percentage on bone marrow biopsy [6]. Considering the clinical background of MM, most clinicians consider the plasma cells to be clonal in origin. Flow cytometry is now available at many centers and has less of inter observer bias in reporting plasma cell percentage [7]. The experts felt that a combination of bone marrow aspirate, trephine biopsy, and flow cytometry should be used in patients of plasma cell dyscrasia and the highest of all the measurements should be considered for the enumeration of the plasma cells.
2. *Cytogenetics/Karyotyping* The availability and standardization of reporting of metaphase cytogenetics in Indian setting is far from ideal and thus its utility is questionable. Besides, there are barriers in the timely transportation of samples to the centers where this investigation is done. Separation/isolation of plasma cells from the marrow is costly and labor intensive. The laboratories don't resort to this as it is not economical. FISH on sorted plasma cells is restricted to some academic centers only. Hence it was consensus that wherever possible FISH should be preferred investigation in all patients with MM at the time of diagnosis [8]. Metaphase cytogenetics has limited value in MM when all the other risk assessment data is available.
3. *Evaluation of M protein* Quantification of M band, serum immunofixation and urine protein electrophoresis (UPEP) should be performed at diagnosis. Most experts felt that it is important to do UPEP, urine immunofixation (UIFE), and BJP on 24 h urinary collection rather than the spot urine in patients with MM. UPEP is not performed routinely in most centers (even academic). The evaluation of BJP or spot urine by dipsticks cannot be an alternative for 24 h UP or prelude to the UPEP. A qualitative UPEP may diagnose free light chain myeloma in cases where sFLC is not done. The reasons for not routinely doing

UPEP include lack of education of the physicians and hematologists/oncologists, cost constraints and difficulty in collecting 24-h urine. Also, it is important to compare the extent of proteinuria at baseline to that on follow up. The possibility of bisphosphonate-induced proteinuria must be entertained in patients who develop increasing proteinuria while showing a response to therapy as assessed by other disease parameters. The 24 h UP estimation is particularly useful in suspected cases of light chain amyloidosis [9.] For BJP testing early morning 150 mL urine can be substituted for 24 h urinary collection to avoid difficulties in the urine collected. Although the necessity of UPEP, UIFE and BJP is questionable in patients who undergo SFLC estimation, however, these parameters continue to be a part of response criteria and are thus required on follow-up. Secondly, some patients with free light chain escape can be picked up using UPEP who have increased excretion of the FLC with normal serum FLC. Also, the availability of the SFLC at different places in India is scarce.

4. *PET-CT* The role of PET-CT at initial diagnostic workup in MM—Experts feel that the role of PET/CT in the presence of lytic lesions is limited, except where the patient has symptoms to suggest a plasmacytoma or extramedullary disease. However, as highlighted earlier, availability and cost remain the issues.
5. *sFLC* SFLC can be avoided if the SIFE and SPEP can identify the type of heavy and light chain at the diagnosis if cost is an issue. The standardization of the platform for SFLC is lacking in our country. The difference between light chain assay and the free light chain assay was emphasized by the experts. The utility of light chain assay beyond the chronic renal failure is doubtful, whereas, in MM, it is mandatory to do free light chain assay at diagnosis.
6. *Immunoglobulin levels* The role of immunoglobulins (Ig) levels in monitoring: Ig levels have a role in the monitoring of IgA or IgD myeloma. Other places where Ig Levels can be used are those patients with frequent infections, where the role of prophylactic IVIG to take care of the immune paresis may be important [9].
7. *Investigation for the cause of Anemia* In a developing country like India, anemia may be multifactorial in origin so a relevant minimal set of investigations (iron profile, RBC indices, peripheral blood smear) for diagnosing the etiology of anemia are required before attributing it solely to MM [9].
8. *Evaluation for associated plasma cell disorders* It is important to keep in mind that monoclonal gammopathies represent a wide spectrum of disorders. Amyloidosis and LCDD should be considered in the differential when patients have significant proteinuria [9].

Treatment of MM

The patients at the time of diagnosis are divided into transplant eligible and transplant ineligible patients. Transplant-eligible patients should not be given melphalan upfront. Use of lenalidomide upfront may compromise stem cell collection after prolonged therapy and in older patients [5]. It was a consensus that wherever possible a triplet with two novel agents should be used as upfront therapy in all patients with MM [5]. Supportive therapy forms a very important component of the overall management of MM.

Consensus on Maintenance Therapy in India

Myeloma being a chronic disease with no cure, it is important to consider some form of continuous therapy, but clinicians are uncertain about the choice and duration of therapy to decrease the relapses. The major issues in India as in other countries are the problems of compliance and toxicity (both physical and economical). The choice of maintenance strategies is dependent on transplant eligibility of a patient.

1. *Maintenance therapy post-transplant* In patients with intermediate or high-risk disease maintenance therapy should be offered to all patients' post-transplant, the choice of maintenance is dictated by the baseline risk status (Intermediate risk – Lenalidomide × 2y, High risk – Bortezomib × 2y, Del 17p − Combination of Lenalidomide with Bortezomib) [10.] Thalidomide is still used in many parts of the country as a choice for maintenance.
2. *Continuous therapy in transplant ineligible patients* Continuous therapy should be considered after attaining a plateau response for at least 2 years (or till clinical or biochemical progression or intolerability) in all patients irrespective of baseline risk status who were either not considered for transplant, ineligible or non-affording for HSCT. Lenalidomide should be used at a dose of 10 mg every 21 days a month and bortezomib should be used at a dose of 1.3 mg/m^2 s/c every 15 days. The choice of maintenance therapy is dictated by the response to the agents used in induction regimen [10]. Currently, the data is premature for using minimal residual disease (MRD) as a guide for the duration of continuous therapy.
3. *Follow up during maintenance therapy* Owing to the resource constraints, the experts suggested a 2 monthly

CBC and biochemistry in patients on maintenance therapy. M protein could be monitored every 3 monthly after attaining plateau stage of response or repeated at a higher frequency if clinically indicated.

Consensus on Transplant in Multiple Myeloma

Even in the era of multiple novel agents, autologous stem cell transplant (ASCT) offers the best PFS and OS benefit to the MM patients. Autologous transplant should be offered to all patients who are eligible and affording for the same.

1. *Barriers for ASCT in Indian scenario* A very small fraction of Indian MM patients are transplanted currently (<5%). The various barriers include scarcity of beds, priority to other life-threatening hematological diseases (acute myeloid leukemia, aplastic anemia etc.), performance status of our patients, financial constraints, lack of adequate, appropriate counseling to the patient and socio-cultural barriers unique to our setting.
2. *The role of Outpatient-Transplant* To fight the bed crisis, international experts suggested the utility of outpatient-transplants, however, most Indian experts were reluctant to accept this as an option. The major inhibitions included lack of understanding of the intensity of care by the patients, complications, need for immediate reporting to the medical facility, and availability of hygienic surroundings for the care of post-transplant patients.
3. *Optimal Conditioning regimen* Melphalan 200 mg/m^2 (Mel-200) is still the preferred regimen for conditioning in most centers, with the abbreviation of melphalan dose to 140 mg/m^2 in the case of renal dysfunction (CrCl < 40 ml/min). BEAM conditioning may be offered to patients with extramedullary disease [11].
4. *Tandem Transplants in India* We have a very scarce experience as far as the tandem transplants are concerned. The reason for it not being routinely utilized being tolerability as well as affordability of our patients. The experts suggested that even in Indian scenarios, tandem transplants may be a consideration in cases of primary plasma cell leukemia, del 17 p, and less than VGPR post-transplant [12].
5. *Allogeneic transplant in MM* The role of allogeneic transplant is dwindling across the world owing to the discovery of newer drugs including monoclonal antibodies and secondly due to lack of overall survival (OS) benefit [13]. Even in India, experts concur with the dwindling role, because of higher transplant related mortality (TRM)/morbidity associated with allogeneic SCT. However, it can still be a last resort in patients with relapsed/refractory MM (RRMM), young individuals with pan-drug resistance, relapse after autologous transplant and del 17 p myeloma. Experts also felt upcoming role of haploidentical stem cell transplant in this setting as the prognosis of this condition is very poor.
6. *Mobilization* In our setting, around 5–18% patients are poor mobilizers [14]. Peripheral blood CD_{34} may be used to guide the use of upfront immediate plerixafor salvage (IPS). Target stem cell harvest is variable between institutes (varying from 2 to 5 million per kg), no clear guidelines are available on the same and practice is extremely heterogeneous. Lenalidomide should be stopped at least 10 days prior to stem cell collection. Usage of lenalidomide (beyond 4 cycles) as part of induction may be myelotoxic, thus impeding stem cell harvest as opined by most experts though there is no clear data to substantiate the same.
7. *Use of G-CSF post-transplant* Most centers use G-CSF post-transplant (starting from D_1 or D_5) to decrease the neutropenic period prior to engraftment. Studies from the west have suggested no utility of G-CSF post-transplant. There are no studies from India to support the usage of G-CSF. International experts suggested abandoning this procedure to decrease both the transplant costs and unnecessary medication post-transplant [15].
8. *Ideal timing for transplant* In our settings, the age of 65 years is taken as the cut-off for transplant at most centers. Patients attaining responses of ≥VGPR are considered eligible for transplant as in the west. Patients who failed to achieve a response better than PR should be considered for second-line therapy [12.]

Consensus on Management of MM with end organ involvement

1. *CNS Myeloma* VRD (Bortezomib, Lenalidomide, dexamethasone) with triple intrathecal therapy (TIT) or with radiotherapy (RT) may be used in patients who present with CNS myeloma. DCEP or DT-PACE followed by RT are alternative options. BEAM conditioning for ASCT may be preferred in patients with CNS disease (active or remote) [16].
2. *Renal failure in Myeloma* In patients with myeloma with cast nephropathy, high cut-off dialysis is still not available at most centers and data for its beneficial role is still lacking. Plasmapheresis may be used in patients who are oliguric or anuric with very high free light chain levels and should be avoided in patients with normal urine output. Optimal induction regimens in

patients of MM with cast nephropathy include CyBorDexThal (VCDT) or BorThalDex (VTD) [17]. Most experts agree that high dose dexamethasone and two novel agents are preferred to be used in patients with cast nephropathy. Experts also agree that if the condition of the patient permit, a fourth drug can be added for the first month of therapy [17].

Consensus on Supportive care in MM

1. *Management of SRE (vertebral compression fracture)* Vertebral Compression fracture is a common complication in patients with MM. Radiation therapy (RT) can be offered for pain relief in transplant ineligible MM patients with vertebral compression fracture with no paraplegia or impending paraplegia. RT is also preferred in patients with paraspinal extramedullary disease or patients who present with inoperable cord compression. Important differentials for paraplegia in MM includes the presence of extramedullary disease (ruled out by sensitive imaging such as PET CT), PIVD, diabetic radicular-neuropathy and drug-related neuropathy. Vertebroplasty and kyphoplasty are still used infrequently in most centers owing to lack of technical expertise and associated costs, however, these techniques can provide considerable pain relief and improved QoL if performed with technical expertise. Multiple vertebral compression fractures are a contraindication to the use of vertebral augmentation procedures. Use of bisphosphonates form an important component of supportive management. Patients should be supplemented with vitamin D3 and calcium along with bisphosphonates [18].
2. *Antimicrobial prophylaxis in patients with MM* Acyclovir is indicated for all patients who are receiving Bortezomib. Routine use of fluoroquinolone/Antibacterial prophylaxis is not recommended in Indian scenario considering the high prevalence of tuberculosis in our country. Prophylaxis is indicated in all patients who are receiving high dose dexamethasone (sulfamethoxazole trimethoprim for PCP and fluconazole as antifungal) [19].
3. *Vaccination in patients with Multiple Myeloma* All patients should be revaccinated between 6 and 12 months posttransplant if the disease is under control. In patients who haven't undergone a transplant, revaccination should be done once they achieve complete remission status. Seasonal influenza vaccination should be offered to all patients with MM annually [20].

Formation of IMAGe

One of the major highlights of the conference was the formal launch of IMAGE (**I**ndian **M**yeloma **A**cademic **G**roup**e**). The purpose of formation of IMAGe is to strengthen research and create awareness about myeloma and related disorders and form consensus guidelines/recommendations that can be adapted to the Indian scenario. A logo was made for the group as shown in Fig. 1. The main aim of IMAGe is to train health care personnel and bring about consensus and homogeneity in the management of MM patients amongst the various health care providers (ranging from neurologists, neurosurgeons, endocrinologists, radiation oncologists, nephrologists, hematologists and various other supportive care team members). Given that published multicentric data of MM patients from India is lacking, IMAGe also importantly aims to collate data and nurture collaboration among institutions regarding the various aspects of MM care.

The recently held conference was successful in collating MM transplant-related data on a common platform. The faculty from various institutions as well as delegates agreed that approximately less than 5% of the eligible population in India undergoes transplant as compared to approximately 40% in the USA. These data highlighted the need to create a working group. The primary objective of this group would be to collate data from all centers within India (both transplant and non-transplant) while maintaining patient/institute confidentiality and ensuring intellectual credit to investigators.

Conclusion

In the era of rapidly changing medical science and advancements, the conference on MM has tried to evolve a consensus on some of the issues that concern the

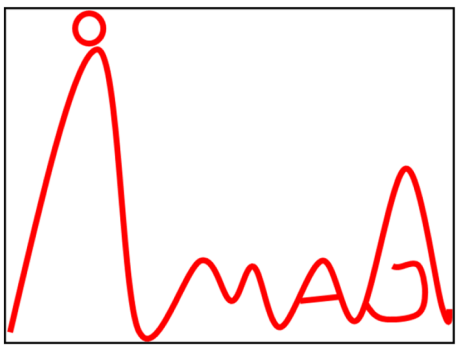

Fig. 1 Logo for IMAGe

management of MM in an Indian setting. These by no means are ideal and all experts agree that much more needs to be done in this field. These proceedings are only a beginning to bringing some uniformity on the diagnosis and treatment of MM in India. With the formation of IMAGe and the IMWG meeting being held in India, these proceeding are geared towards initiating a MM registry in India. They are also focused on igniting prospective research and encouraging the next generation of hematologist/oncologist to actively participate in MM research. It is the recommendation of the expert panel that a single theme myeloma conference such as this should be held every 2-years to continue the momentum noted with this meeting.

IMAGE Group Abhay Bhave, Mumbai; Ajay Sharma, Sir Gangaram Hospital, New Delhi; A.K.Tripathi, KGMU, Lucknow;Alka Khadwal, PGIMER, Chandigarh; Anil Aribandi, American Oncology, Hyderabad; Anita Ramesh, Saveetha Medical College Hospital, Chennai; Ashish Dixit, Manipal Hospital, Bengalaru; Anup J Devasia, CMC Vellore; Charu Batra, Karnal, Chezhian Subash, MIOT, Chennai; Dharma Choudhary, BL Kapoor Hospital, New Delhi, Dinesh Bhurani, Rajiv Gandhi Cancer Center, New Delhi; Deepesh Lad, PGIMER, Chandigarh; Farah Jijina, PD Hinduja Hospital, Mumbai; Gaurav Prakash, PGIMER, Chandigarh; Ganesh Jaishetwar, Yashoda Hospital, Hyderabad; Wg Cdr Harshit Khurana, Command Hospital, Bengalaru; Hemant Malhotra, SMS Jaipur; H.S. Kohli, PGIMER, Chandigarh; Ian Pinto, Reliance Foundation, Mumbai; Javid Rasool, SKIMS, Srinagar, Jatin Sarin, IVY Hospital, Mohali; Jina Bhattacharyya, Medical Collegue, Guwahati; Col Jasjit Singh, Command Hospital, Chandigarh; K Govind Babu, Kidwai Memorial Institute of Oncology; K Pavithran, Amrita Institute, Kochi; Kannan Subramanian, Sahaydari Hospital, Pune; M Joseph John, CMC, Ludhiana; Man Updesh Singh Sachdeva, PGIMER, Chandigarh; Maitreyee Bhattacharyya, MC Kolkata, Kolkata, MB Agarwal, Bombay Hospital, Mumbai; Manju Sengar, TMH, Mumbai, Narender Kumar, PGIMER, Chandigarh; Nitin Sood, Medanta Hospital, New Delhi; Prantar Chakravarti, NRS Medical College, Kolkata, PG Subramanian, TMH, Mumbai; Prashant Sharma, PGIMER, Chandigarh; Prashant Tembhare, TMH, Mumbai; Pravas Mishra, AIIMS, New Delhi, Prasanth Ganesan, Cancer Institute Adiyar, Chennai, Rahul Naithani, Max Hospital, New Delhi; Rayaz Ahmed, RCGI, New Delhi; Ritu Gupta, IRCH, AIIMS, New Delhi; Ritu Bansal, PGIMER, Chandigarh; Ritambhra Nada, PGIMER, Chandigarh; Raman Arora, Oswal Hospital, Ludhiana; Col Rajan Kapoor, Army Hospital (R&R), New Delhi; Reena Das, PGIMER, Chandigarh; Reena Nair, TMC, Kolkata; Sandeep Shah, GCRI, Ahmedabad, Savita Kumari, PGIMER, Chandigarh; Sharat Damodar, Mazumdar Cancer Center, Bengalaru; Sachin Gupta, Max Hospital, Mohali, Sameer Melinkeri, Deenanath Mangeshkar Hospital, Pune; Shano Naseem, PGIMER, Chandigarh, Sreejesh Sreedharanunni, PGIMER, Chandigarh Suparno Chakrabarti, DHRC, New Delhi; Sadashivudu Gundeti, NIMS, Hyderabad; Surg Capt S Das, Army Hospital (R&R) Hospital, New Delhi,Soniya Nityanand, SGPGI, Lucknow; Seema Bhatwadekar, Sterling Hospital, Vadodra; Shankar Prinja, PGIMER, Chandigarh; Tejinder Singh, Onquest Laboratories, New Delhi; Vikas Suri, PGIMER, Chandigarh; Lt Gen Velu Nair, Army Hospital (R&R), New Delhi.

References

1. Reddy KS (2015) India's aspirations for Universal Health coverage. N Engl J Med 373(1):1–5
2. Wadhera RK, Rajkumar SV (2010) Prevalence of monoclonal gammopathy of undetermined significance: a systematic review. Mayo Clin Proc 85(10):933–942
3. Meher Lakshmi Konatam AP, Sadashivudu G (2016) Age of onset of multiple myeloma: a Paradigm shift in Indian patients Indian. J Appl Res 6(10):3
4. Smith RA, Manassaram-Baptiste D, Brooks D, Doroshenk M, Fedewa S, Saslow D et al (2015) Cancer screening in the United States, 2015: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 65(1):30–54
5. Rajkumar SV (2016) Myeloma today: disease definitions and treatment advances. Am J Hematol 91(1):90–100
6. Al-Quran SZ, Yang L, Magill JM, Braylan RC, Douglas-Nikitin VK (2007) Assessment of bone marrow plasma cell infiltrates in multiple myeloma: the added value of CD138 immunohistochemistry. Hum Pathol 38(12):1779–1787
7. Paiva B, Vidriales MB, Perez JJ, Mateo G, Montalban MA, Mateos MV et al (2009) Multiparameter flow cytometry quantification of bone marrow plasma cells at diagnosis provides more prognostic information than morphological assessment in myeloma patients. Haematologica 94(11):1599–1602
8. Rajan AM, Rajkumar SV (2015) Interpretation of cytogenetic results in multiple myeloma for clinical practice. Blood Cancer J 5:e365
9. Dimopoulos M, Kyle R, Fermand JP, Rajkumar SV, San Miguel J, Chanan-Khan A et al (2011) Consensus recommendations for standard investigative workup: report of the International Myeloma Workshop Consensus Panel 3. Blood 117(18):4701–4705
10. Facon T (2015) Maintenance therapy for multiple myeloma in the era of novel agents. Hematol Am Soc Hematol Educ Prog 2015:279–285
11. Moreau P, Attal M, Facon T (2015) Frontline therapy of multiple myeloma. Blood 125(20):3076–3084
12. Gertz MA, Dingli D (2014) How we manage autologous stem cell transplantation for patients with multiple myeloma. Blood 124(6):882–890
13. Dhakal B, Vesole DH, Hari PN (2016) Allogeneic stem cell transplantation for multiple myeloma: is there a future? Bone Marrow Transp 51(4):492–500
14. Kumar L, Raju GM, Ganessan K, Shawgi S, Menon H, Wadhwa J et al (2003) High dose chemotherapy followed by autologous haemopoietic stem cell transplant in multiple myeloma. Natl Med J India 16(1):16–21
15. Trivedi M, Martinez S, Corringham S, Medley K, Ball ED (2009) Optimal use of G-CSF administration after hematopoietic SCT. Bone Marrow Transp 43(12):895–908
16. Chen C, Rabea AM, Masih-Khan E, Chu C-M, Kukreti V, Trudel S et al (2011) Central Nervous System (CNS) Involvement with Multiple Myeloma (MM)–Longterm Survival Can Be Achieved with Radiation, Intrathecal (IT) Chemotherapy, and Immunomodulatory Agents (IMiDs). Blood. 118(21):3983
17. Dimopoulos MA, Sonneveld P, Leung N, Merlini G, Ludwig H, Kastritis E et al (2016) International myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol 34(13):1544–1557
18. Silbermann R, Roodman GD (2013) Myeloma bone disease: pathophysiology and management. J Bone Oncol 2(2):59–69

19. Vesole DH, Oken MM, Heckler C, Greipp PR, Katz MS, Jacobus S et al (2012) Oral antibiotic prophylaxis of early infection in multiple myeloma: a URCC/ECOG randomized phase III study. Leukemia 26(12):2517–2520

20. Alemu A, Richards JO, Oaks MK, Thompson MA (2016) Vaccination in multiple myeloma: review of current literature. Clin Lymphoma Myeloma Leuk 16(9):495–502