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Introductory Chapter: Multiple Myeloma in the Era of Novel Therapeutics

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1. Introduction

Multiple myeloma (MM), the second most common hematologic malignancy (HM), is a malignant B-cell neoplasm that is characterized by clonal expansion of plasma cells in the bone marrow (BM) with subsequent production of monoclonal immunoglobulins [1–8]. The disease has several complications including anemia; renal dysfunction or failure; bone involvement including osteopenia, lytic lesions, and pathological fractures; hypercalcemia; immunodeficiency; and various infectious complications [1, 4, 5, 7–12]. The incidence of MM has increased since the year 1990 with the largest increase in resource-poor countries [13]. MM is a heterogeneous disease even in its etiology, and there are several risk factors for the disease that include old age; obesity; ionizing radiation; exposure to solvents and pesticides; agricultural occupations; autoimmune disorders such as pernicious anemia and ankylosing spondylitis; monoclonal gammopathy of undetermined significance; and familial predisposition [14–18]. One hallmark of MM is the presence of heterogeneous chromosomal aberrations and numerous genetic mutations that not only can help in risk stratifying the disease but also can affect management and prognosis to a large extent [7, 8, 19]. Recently, MM is stratified according to stage of the disease, plasma cell labeling index, cytogenetics, and gene expression profiling [20–22].

Over the past two decades, the outcomes of patients with MM have improved substantially even in patients with relapsed or refractory (RR) disease [1–4, 23–28]. The remarkable improvement in the outcome of MM is due to the following reasons: (1) the evolution of advanced technology that facilitated understanding biology of the disease and helped in the diagnosis, risk stratification, and follow-up of patients; (2) the introduction of several novel therapies, monoclonal antibodies, and immunotherapies; (3) the widespread utilization of high-dose (HD) chemotherapy followed by autologous stem cell transplantation (HSCT); (4) the recent improvements in supportive care and antimicrobial therapies; and (5) the evolution of new

therapeutic strategies such as consolidation and maintenance treatments as well as total or continuous therapy [1–5, 24–29]. Currently, the following novel therapies are available for patients with MM: (1) immunomodulatory agents such as thalidomide, lenalidomide, and pomalidomide; (2) proteasome inhibitors such as bortezomib, carfilzomib, and ixazomib; (3) monoclonal antibodies such as daratumumab and elotuzumab; and (4) histone deacetylase inhibitors such as panobinostat and vorinostat [1–5, 26–29]. Other novel therapeutic options that are available for patients with RR-MM include chimeric antigen receptor T cells as well as other cellular and immunotherapies such as the use of specific antigen-presenting cells to overcome immune incompetence and engineered T cells as well as natural killer cell products [30–32].

Several studies and meta-analyses have shown that the most beneficial induction therapies in terms of overall response rate, overall survival (OS), and progression-free survival (PFS) in transplant-eligible patients with newly diagnosed MM are (1) bortezomib, lenalidomide, and dexamethasone (VRD), (2) bortezomib, cyclophosphamide, and dexamethasone, and (3) bortezomib, thalidomide, and dexamethasone [1, 33–35]. However, the standard induction therapy in patients with newly diagnosed MM is the VRD triplet regimen [4, 8]. Also, autologous HSCT is the standard of care for transplant eligible patients either upfront or at relapse [4, 8, 27]. Therefore, HD chemotherapy followed by autologous HSCT, which is an integral part in the treatment of the disease, is considered the standard of care for patients with MM who are eligible for HSCT [36–39]. With the recent advances in supportive care, autologous HSCT has been extended to include older patients with MM and those with comorbid medical conditions such as renal failure (RF) [37, 38]. Nevertheless, autologous HSCT and novel therapies are complementary to each other in the management of patients with MM [37, 40].

Studies have shown that post-HSCT consolidation and maintenance treatments can further improve the outcome of patients with MM [8, 27, 41]. In particular, the use of either proteasome inhibitors such as bortezomib or immunomodulatory drugs such as lenalidomide in the maintenance therapy is associated with increased OS and PFS [42–46]. However, for transplant-eligible patients, stratified maintenance therapy based on risk features and depth of response is recommended [47]. Monitoring disease response at various stages of treatment is essential, and studies have shown that monitoring of minimal residual disease (MRD) is associated with longer PFS and OS [48, 49]. Patients with high-risk (HR) cytogenetics require not only specific induction therapies but also autologous HSCT as well as consolidation and maintenance therapies [50, 51]. For such patients, deeper responses should be obtained as several studies and meta-analyses have shown that MRD negativity is a strong predictor of clinical outcome and is associated with long-term survival [49, 52, 53].

The numerous treatment modalities that are available for patients with MM have shown their efficacy, but they have their own adverse effects that include BM suppression and infectious complications that may be life-threatening [9, 10, 54].

Also, there is very limited access to effective care in many countries particularly in sub-Saharan Africa. Additionally, the available novel therapies are rather expensive, and the economic burden of the disease is huge [13, 14, 55–57].

Progression of MM is related to the underlying BM microenvironment and to the genetic heterogeneity of the disease [7, 19]. Studies have shown that the main causes of death in patients with MM are infections, comorbid medical conditions such as RF, having RR disease, and the presence

of HR features such as adverse cytogenetics or advanced stage of the disease at presentation [54, 58, 59]. The second-line treatment for patients with RR-MM is rather heterogeneous [60]. Different novel therapeutic agents that are usually given in various combinations are currently available for the treatment of patients with RR disease [61, 62]. However, in the setting of RR disease, treatment options become more complex, but the aim should be to provide the patient with specific drug combination so as to gain clinical benefit while minimizing drug toxicity [63]. Additionally, studies have shown clinical benefit for continued therapy. However, improved outcome is paralleled by certain barriers such as drug toxicity and evolution of drug resistance [64, 65].

Current treatment standards for patients with RR-MM include (1) salvage therapy using a combination of novel agents, (2) salvage autologous HSCT, (3) allogeneic HSCT in highly selected patients with RR-MM, and (4) post-HSCT consolidation and maintenance therapies [39, 66–68]. The available novel drug combinations that have been shown to be effective in RR disease include (1) daratumumab, lenalidomide, and dexamethasone, (2) daratumumab, bortezomib, and dexamethasone, (3) carfilzomib-based combinations with panobinostat or elotuzumab, and (4) pomalidomide-based combinations with carfilzomib or dexamethasone [24, 66, 69–72]. However, the choice of therapeutic regimen should take disease-related factors and patient-related factors into consideration [62, 63, 73].

Life expectancy in patients with MM has recently increased due to the availability of large numbers of novel agent with different mechanisms of action against the disease [3, 24, 27, 74]. For example, in the year 2015, five new novel agents were approved for the treatment of RR-MM [24]. Unfortunately, despite the progress achieved in the diagnostics and therapeutics including the plethora of new novel agents and despite the remarkable improvements in supportive care and stem cell therapies, the disease remains mostly incurable as patients usually experience disease relapse after enjoying a certain period of disease control [1, 3–5, 24, 28, 74, 75].

Hopefully, the following will optimize antimyeloma management in the near future: (1) better understanding of the biology of the disease, (2) characterization of genetic and molecular basis of the disease, (3) incorporation of risk stratification in the management of newly diagnosed MM patients, (4) availability of several novel agents as well as monoclonal antibodies and effective management of their adverse effects, (5) availability of safer autologous HSCT, (6) improvement of supportive care and management of comorbid medical conditions, and (7) designing new novel therapies to restore autologous antimyeloma immunity and to target protein degradation as well as aberrant biology [4, 65, 76–78]. Finally, it is essential to reduce the costs of the novel therapies so that patients with low income can afford them and make benefit from utilizing them particularly in the setting of RR-MM [13, 79–81].

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References

- [1] Naymagon L, Abdul-Hay M. Novel agents in the treatment of multiple myeloma: A review about the future. *Journal of Hematology & Oncology*. 2016;**9**(1):52. DOI: 10.1186/s13045-016-0282-1
- [2] Holstein SA, McCarthy PL. Immunomodulatory drugs in multiple myeloma: Mechanisms of action and clinical experience. *Drugs*. 2017;**77**(5):505-520. DOI: 10.1007/s40265-017-0689-1
- [3] Larocca A, Mina R, Gay F, Bringhen S, Boccadoro M. Emerging drugs and combinations to treat multiple myeloma. *Oncotarget*. 2017;**8**(36):60656-60672. DOI: 10.18632/oncotarget.19269. eCollection 2017 Sep 1
- [4] Raza S, Safyan RA, Rosenbaum E, Bowman AS, Lentzsch S. Optimizing current and emerging therapies in multiple myeloma: A guide for the hematologist. *Therapeutic Advances in Hematology*. 2017;**8**(2):55-70. DOI: 10.1177/2040620716680548. Epub 2016 Dec 9
- [5] Mimura N, Hideshima T, Anderson KC. Novel therapeutic strategies for multiple myeloma. *Experimental Hematology*. 2015;**43**(8):732-741. DOI: 10.1016/j.exphem.2015.04.010. Epub 2015 Jun 26
- [6] Rajkumar SV, Kumar S. Multiple myeloma: Diagnosis and treatment. *Mayo Clinic Proceedings*. 2016;**91**(1):101-119. DOI: 10.1016/j.mayocp.2015.11.007
- [7] Fairfield H, Falank C, Avery L, Reagan MR. Multiple myeloma in the marrow: Pathogenesis and treatments. *Annals of the New York Academy of Sciences*. 2016;**1364**:32-51. DOI: 10.1111/nyas.13038
- [8] Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. *American Journal of Hematology*. 2016;**91**(7):719-734. DOI: 10.1002/ajh.24402
- [9] Nucci M, Anaissie E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. *Clinical Infectious Diseases*. 2009;**49**(8):1211-1225. DOI: 10.1086/605664
- [10] Teh BW, Harrison SJ, Worth LJ, Spelman T, Thursky KA, Slavin MA. Risks, severity and timing of infections in patients with multiple myeloma: A longitudinal cohort study in the era of immunomodulatory drug therapy. *British Journal of Haematology*. 2015;**171**(1):100-108. DOI: 10.1111/bjh.13532. Epub 2015 Jun 24
- [11] Heher EC, Rennke HG, Laubach JP, Richardson PG. Kidney disease and multiple myeloma. *Clinical Journal of the American Society of Nephrology*. 2013;**8**(11):2007-2017. DOI: 10.2215/CJN.12231212. Epub 2013 Jul 18
- [12] Katagiri D, Noiri E, Hinoshita F. Multiple myeloma and kidney disease. *Scientific World Journal*. 2013;**2013**:487285. DOI: 10.1155/2013/487285. eCollection 2013
- [13] Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, et al. Global burden of multiple myeloma: A systematic analysis for the global burden of disease study 2016. *JAMA Oncology*. 2018;**4**(9):1221-1227. DOI: 10.1001/jamaoncol.2018.2128. Epub 2018 May 16

- [14] Curado MP, Oliveira MM, Silva DRM, Souza DLB. Epidemiology of multiple myeloma in 17 Latin American countries: An update. *Cancer Medicine*. 2018;**7**(5):2101-2108. DOI: 10.1002/cam4.1347. Epub 2018 Mar 24
- [15] Becker N. Epidemiology of multiple myeloma. *Recent Results in Cancer Research*. 2011;**183**:25-35. DOI: 10.1007/978-3-540-85772-3_2
- [16] Sargentanis TN, Zagouri F, Tsilimidos G, Tsagianni A, Tseliou M, Dimopoulos MA, et al. Risk factors for multiple myeloma: A systematic review of meta-analyses. *Clinical Lymphoma, Myeloma & Leukemia*. 2015;**15**(10):563-577.e1-563-577.e3. DOI: 10.1016/j.clml.2015.06.003. Epub 2015 Jun 19
- [17] Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. *Seminars in Oncology*. 2016;**43**(6):676-681. DOI: 10.1053/j.seminoncol.2016.11.004. Epub 2016 Nov 10
- [18] Raluy M, Ramagopalan S, Panjabi S, Lambrelli D. Epidemiology and clinical characteristics of patients with multiple myeloma in the United Kingdom. *Blood*. 2014;**124**:2048
- [19] Shay G, Hazlehurst L, Lynch CC. Dissecting the multiple myeloma-bone microenvironment reveals new therapeutic opportunities. *Journal of Molecular Medicine*. 2016;**94**(1): 21-35. DOI: 10.1007/s00109-015-1345-4. Epub 2015 Oct 1
- [20] Hanbali A, Hassanein M, Rasheed W, Aljurf M, Alsharif F. The evolution of prognostic factors in multiple myeloma. *Advances in Hematology*. 2017;**2017**:4812637. DOI: 10.1155/2017/4812637. Epub 2017 Feb 21
- [21] Johnson SK, Heuck CJ, Albino AP, Qu P, Zhang Q, Barlogie B, et al. The use of molecular-based risk stratification and pharmacogenomics for outcome prediction and personalized therapeutic management of multiple myeloma. *International Journal of Hematology*. 2011;**94**(4):321-333. DOI: 10.1007/s12185-011-0948-y. Epub 2011 Oct 15
- [22] Chng WJ, Dispenzieri A, Chim CS, Fonseca R, Goldschmidt H, Lentzsch S, et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014;**28**(2):269-277. DOI: 10.1038/leu.2013.247. Epub 2013 Aug 26
- [23] Thorsteinsdottir S, Dickman PW, Landgren O, Blimark C, Hultcrantz M, Turesson I, et al. Dramatically improved survival in multiple myeloma patients in the recent decade: Results from a Swedish population-based study. *Haematologica*. 2018;**103**(9):e412-e415. DOI: 10.3324/haematol.2017.183475. Epub ahead of print
- [24] Dingli D, Ailawadhi S, Bergsagel PL, Buadi FK, Dispenzieri A, Fonseca R, et al. Therapy for relapsed multiple myeloma: Guidelines from the Mayo stratification for myeloma and risk-adapted therapy. *Mayo Clinic Proceedings*. 2017;**92**(4):578-598. DOI: 10.1016/j.mayocp.2017.01.003. Epub 2017 Mar 11
- [25] Kharfan-Dabaja MA, Hamadani M, Reljic T, Nishihori T, Bensinger W, Djulbegovic B, et al. Comparative efficacy of tandem autologous versus autologous followed by allo geneic hematopoietic cell transplantation in patients with newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. *Journal of Hematology & Oncology*. 2013;**6**:2. DOI: 10.1186/1756-8722-6-2

- [26] Anderson KC. Progress and paradigms in multiple myeloma. *Clinical Cancer Research*. 2016;**22**(22):5419-5427. DOI: 10.1158/1078-0432.CCR-16-0625
- [27] Gay F, Engelhardt M, Terpos E, Wäsch R, Giaccone L, Auner HW, et al. From transplant to novel cellular therapies in multiple myeloma: European myeloma network guidelines and future perspectives. *Haematologica*. 2018;**103**(2):197-211. DOI: 10.3324/haematol.2017.174573. Epub 2017 Dec 7
- [28] Sonneveld P, De Wit E, Moreau P. How have evolutions in strategies for the treatment of relapsed/refractory multiple myeloma translated into improved outcomes for patients? *Critical Reviews in Oncology/Hematology*. 2017;**112**:153-170. DOI: 10.1016/j.critrevonc.2017.02.007. Epub 2017 Feb 14
- [29] Orlowski RZ, Lonial S. Integration of novel agents into the care of patients with multiple myeloma. *Clinical Cancer Research*. 2016;**22**(22):5443-5452. DOI: 10.1158/1078-0432.CCR-16-0861. Epub 2016 Nov 14
- [30] Garfall AL, Stadtmauer EA, Hwang WT, Lacey SF, Melenhorst JJ, Krevvata M, et al. Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma. *JCI Insight*. 2018;**3**(8):pii: 120505. DOI: 10.1172/jci.insight.120505. Epub ahead of print
- [31] Danylesko I, Beider K, Shimoni A, Nagler A. Novel strategies for immunotherapy in multiple myeloma: Previous experience and future directions. *Clinical & Developmental Immunology*. 2012;**2012**:753407. DOI: 10.1155/2012/753407. Epub 2012 May 10
- [32] Rasche L, Weinhold N, Morgan GJ, van Rhee F, Davies FE. Immunologic approaches for the treatment of multiple myeloma. *Cancer Treatment Reviews*. 2017;**55**:190-199. DOI: 10.1016/ctrv.2017.03.010. Epub 2017 Apr 6
- [33] Wang X, Li Y, Yan X. Efficacy and safety of novel agent-based therapies for multiple myeloma: A meta-analysis. *BioMed Research International*. 2016;**2016**:6848902. DOI: 10.1155/2016/6848902. Epub 2016 Feb 1
- [34] Zeng ZH, Chen JF, Li YX, Zhang R, Xiao LF, Meng XY. Induction regimens for transplant-eligible patients with newly diagnosed multiple myeloma: A network meta-analysis of randomized controlled trials. *Cancer Management and Research*. 2017;**9**:287-298. DOI: 10.2147/CMAR.S138932. eCollection 2017
- [35] Kouroukis TC, Baldassarre FG, Haynes AE, Imrie K, Reece DE, Cheung MC. Bortezomib in multiple myeloma: Systematic review and clinical considerations. *Current Oncology*. 2014;**21**(4):e573-e603. DOI: 10.3747/co.21.1798
- [36] Al-Anazi KA. Autologous hematopoietic stem cell transplantation for multiple myeloma without cryopreservation. *Bone Marrow Research*. 2012;**2012**:917361. DOI: 10.1155/2012/917361. Epub 2012 May 28
- [37] Costa LJ, Zhang MJ, Zhong X, Dispenzieri A, Lonial S, Krishnan A, et al. Trends in utilization and outcomes of autologous transplantation as early therapy for multiple myeloma. *Biology of Blood and Marrow Transplantation*. 2013;**19**(11):1615-1624. DOI: 10.1016/j.bbmt.2013.08.002. Epub 2013 Aug 11

- [38] Mahajan S, Tandon N, Kumar S. The evolution of stem-cell transplantation in multiple myeloma. *Therapeutic Advances in Hematology*. 2018;**9**(5):123-133. DOI: 10.1177/2040620718761776. Epub 2018 Mar 5
- [39] Mactier CE, Islam MS. Haematopoietic stem cell transplantation as first-line treatment in myeloma: A global perspective of current concepts and future possibilities. *Oncology Reviews*. 2012;**6**(2):e14. DOI: 10.4081/oncol.2012.e14. eCollection 2012 Oct 2
- [40] Cavo M. A third-generation IMiD for MM. *Blood*. 2011;**118**(11):2931-2932. DOI: 10.1182/blood-2011-07-364315
- [41] Facon T. Maintenance therapy for multiple myeloma in the era of novel agents. *Hematology. American Society of Hematology. Education Program*. 2015;**2015**:279-285. DOI: 10.1182/asheducation-2015.1.279
- [42] Ye X, Huang J, Pan Q, Li W. Maintenance therapy with immunomodulatory drugs after autologous stem cell transplantation in patients with multiple myeloma: A meta-analysis of randomized controlled trials. *PLoS One*. 2013;**8**(8):e72635. DOI: 10.1371/journal.pone.0072635. eCollection 2013
- [43] Lee HS, Min CK. Optimal maintenance and consolidation therapy for multiple myeloma in actual clinical practice. *The Korean Journal of Internal Medicine*. 2016;**31**(5):809-819. DOI: 10.3904/kjim.2016. 110. Epub 2016 Sep 1
- [44] Li J-L, Fan G-Y, Liu Y-J, Zeng Z-H, Huang J-J, Yang Z-M, et al. Long-term efficacy of maintenance therapy for multiple myeloma: A quantitative synthesis of 22 randomized controlled trials. *Frontiers in Pharmacology*. 2018;**9**:430. DOI: 10.3389/fphar.2018.00430. Epub 2018 Apr 30
- [45] Mian I, Milton DR, Shah N, Nieto Y, Popat UR, Kebriaei P, et al. Prolonged survival with a longer duration of maintenance lenalidomide after autologous hematopoietic stem cell transplantation for multiple myeloma. *Cancer*. 2016;**122**(24):3831-3837. DOI: 10.1002/cncr.30366. Epub 2016 Sep 28
- [46] Liu J, Yang H, Liang X, Wang Y, Hou J, Liu Y, et al. Meta-analysis of the efficacy of treatments for newly diagnosed and relapsed/refractory multiple myeloma with del(17p). *Oncotarget*. 2017;**8**(37):62435-62444. DOI: 10.18632/oncotarget.18722. eCollection 2017 Sep 22
- [47] Lipe B, Vukas R, Mikhael J. The role of maintenance therapy in multiple myeloma. *Blood Cancer Journal*. 2016;**6**(10):e485. DOI: 10.1038/bcj.2016.89
- [48] Landgren O, Rajkumar SV. New developments in diagnosis, prognosis, and assessment of response in multiple myeloma. *Clinical Cancer Research*. 2016;**22**(22):5428-5433. DOI: 10.1158/1078-0432.CCR-16-0866
- [49] Fulciniti M, Munshi NC, Martinez-Lopez J. Deep response in multiple myeloma: A critical review. *BioMed Research International*. 2015;**2015**:832049. DOI: 10.1155/2015/832049. Epub 2015 Dec 10
- [50] Sonneveld P, Avet-Loiseau H, Lonial S, Usmani S, Siegel D, Anderson KC, et al. Treatment of multiple myeloma with high-risk cytogenetics: A consensus of the International Myeloma

- Working Group. *Blood*. 2016;**127**(24):2955-2962. DOI: 10.1182/blood-2016-01-631200. Epub 2016 Mar 21
- [51] Kazmi SM, Nusrat M, Gunaydin H, Cornelison AM, Shah N, Kebriaei P, et al. Outcomes among high-risk and standard-risk multiple myeloma patients treated with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation. *Clinical Lymphoma, Myeloma & Leukemia*. 2015;**15**(11):687-693. DOI: 10.1016/j.clml. 2015.07.641. Epub 2015 Aug 5
- [52] Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: A meta-analysis. *Bone Marrow Transplantation*. 2016;**51**(12):1565-1568. DOI: 10.1038/bmt.2016. 222. Epub 2016 Sep 5
- [53] Munshi NC, Avet-Loiseau H, Rawstron AC, Owen RG, Child JA, Thakurta A, et al. Association of minimal residual disease with superior survival outcomes in patients with multiple myeloma: A meta-analysis. *JAMA Oncology*. 2017;**3**(1):28-35. DOI: 10.1001/jamaoncol.2016.3160
- [54] Mai EK, Haas EM, Lücke S, Löpprich M, Kunz C, Pritsch M, et al. A systematic classification of death causes in multiple myeloma. *Blood Cancer Journal*. 2018;**8**(3):30. DOI: 10.1038/s41408-018-0068-5
- [55] MacEwan JP, Batt K, Yin W, Peneva D, Sison S, Vine S, et al. Economic burden of multiple myeloma among patients in successive lines of therapy in the United States. *Leukemia & Lymphoma*. 2018;**59**(4):941-949. DOI: 10.1080/10428194. 2017.1361035. Epub 2017 Aug 13
- [56] Robinson D Jr, Orlowski RZ, Stokes M, He J, Huse S, Chitnis A, et al. Economic burden of relapsed or refractory multiple myeloma: Results from an international trial. *European Journal of Haematology*. 2017;**99**(2):119-132. DOI: 10.1111/ejh.12876. Epub 2017 May 11
- [57] Pandya S, Clancy Z, Shrestha S, Wang L, Ni Q, Baser O. Economic burden of early progression in newly-diagnosed multiple myeloma patients. *Journal of Clinical Oncology*. 2018;**36**(15 suppl):e20040. DOI: 10.1200/JCO.2018.36.15_suppl.e20040. Epub 2018 June 01
- [58] Gregersen H, Vangsted AJ, Abildgaard N, Andersen NF, Pedersen RS, Frølund UC, et al. The impact of comorbidity on mortality in multiple myeloma: A Danish nationwide population-based study. *Cancer Medicine*. 2017;**6**(7):1807-1816. DOI: 10.1002/cam4.1128. Epub 2017 Jun 22
- [59] Blimark C, Holmberg E, Mellqvist UH, Landgren O, Björkholm M, Hultcrantz M, et al. Multiple myeloma and infections: A population-based study on 9253 multiple myeloma patients. *Haematologica*. 2015;**100**(1):107-113. DOI: 10.3324/haematol.2014.107714. Epub 2014 Oct 24
- [60] Jagannath S, Abonour R, Durie BGM, Gasparetto C, Hardin JW, Narang M, et al. Heterogeneity of second-line treatment for patients with multiple myeloma in the connect MM registry (2010-2016). *Clinical Lymphoma, Myeloma & Leukemia*. 2018;**18**(7):480-485.e3. DOI: 10.1016/j.clml.2018.04.007. Epub 2018 May 4

- [61] Botta C, Ciliberto D, Rossi M, Staropoli N, Cucè M, Galeano T, et al. Network meta-analysis of randomized trials in multiple myeloma: Efficacy and safety in relapsed/refractory patients. *Blood Advances*. 2017;**1**(7):455-466. DOI: 10.1182/bloodadvances.2016003905. eCollection 2017 Feb 28
- [62] Nijhof IS, van de Donk NWCJ, Zweegman S, Lokhorst HM. Current and new therapeutic strategies for relapsed and refractory multiple myeloma: An update. *Drugs*. 2018;**78**(1):19-37. DOI: 10.1007/s40265-017-0841-y
- [63] Cook G, Zweegman S, Mateos MV, Suzan F, Moreau P. A question of class: Treatment options for patients with relapsed and/or refractory multiple myeloma. *Critical Reviews in Oncology/Hematology*. 2018;**121**:74-89. DOI: 10.1016/j.critrevonc.2017.11.016. Epub 2017 Dec 5
- [64] Hari P, Romanus D, Palumbo A, Luptakova K, Rifkin RM, Tran LM, et al. Prolonged duration of therapy is associated with improved survival in patients treated for relapsed/refractory multiple myeloma in routine clinical care in the United States. *Clinical Lymphoma, Myeloma & Leukemia*. 2018;**18**(2):152-160. DOI: 10.1016/j.clml.2017.12.012. Epub 2018 Jan 5
- [65] Ludwig H, Delforge M, Facon T, Einsele H, Gay F, Moreau P, et al. Prevention and management of adverse events of novel agents in multiple myeloma: A consensus of the European myeloma network. *Leukemia*. 2018;**32**(7):1542-1560. DOI: 10.1038/s41375-018-0040-1. Epub 2018 May 2
- [66] Chen R, Wang Y, Luan C, Gao C, Zhang X, Chen B. Effect of pomalidomide on relapsed/refractory multiple myeloma: A systematic review and meta-analysis. *Journal of Cancer*. 2017;**8**(10):1801-1808. DOI: 10.7150/jca.17999. eCollection 2017
- [67] Giralt S, Garderet L, Durie B, Cook G, Gahrton G, Bruno B, et al. American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group consensus conference on salvage hematopoietic cell transplantation in patients with relapsed multiple myeloma. *Biology of Blood and Marrow Transplantation*. 2015;**21**(12):2039-2051. DOI: 10.1016/j.bbmt.2015.09.016. Epub 2015 Sep 30
- [68] Yin X, Tang L, Fan F, Jiang Q, Sun C, Hu Y. Allogeneic stem-cell transplantation for multiple myeloma: A systematic review and meta-analysis from 2007 to 2017. *Cancer Cell International*. 2018;**18**:62. DOI: 10.1186/s12935-018-0553-8. eCollection 2018
- [69] Dimopoulos MA, Kaufman JL, White D, Cook G, Rizzo M, Xu Y, et al. A comparison of the efficacy of immunomodulatory-containing regimens in relapsed/refractory multiple myeloma: A network meta-analysis. *Clinical Lymphoma, Myeloma & Leukemia*. 2018;**18**(3):163-173.e6. DOI: 10.1016/j.clml.2017.12.011. Epub 2018 Jan 5
- [70] Liu L, Zhao N, Xu W, Sheng Z, Wang L. Pooled analysis of the reports of carfilzomib, panobinostat, and elotuzumab combinations in patients with refractory/relapsed multiple myeloma. *Journal of Hematology & Oncology*. 2016;**9**(1):54. DOI: 10.1186/s13045-016-0286-x

- [71] Zou Y, Ma X, Yu H, Hu C, Fan L, Ran X. Carfilzomib/pomalidomide single-agent or in combination with other agents for the management of relapsed/refractory multiple myeloma: A meta-analysis of 37 trials. *Oncotarget*. 2017;**8**(24):39805-39817. DOI: 10.18632/oncotarget.10768
- [72] Zhang T, Wang S, Lin T, Xie J, Zhao L, Liang Z, et al. Systematic review and meta-analysis of the efficacy and safety of novel monoclonal antibodies for treatment of relapsed/refractory multiple myeloma. *Oncotarget*. 2017;**8**(20):34001-34017. DOI: 10.18632/oncotarget.16987
- [73] Cornell RF, Kassim AA. Evolving paradigms in the treatment of relapsed/refractory multiple myeloma: Increased options and increased complexity. *Bone Marrow Transplantation*. 2016;**51**(4):479-491. DOI: 10.1038/bmt.2015.307. Epub 2016 Jan 4
- [74] Gonsalves WI, Milani P, Derudas D, Buadi FK. The next generation of novel therapies for the management of relapsed multiple myeloma. *Future Oncology*. 2017;**13**(1):63-75. DOI: 10.2217/fon-2016-0200. Epub 2016 Aug 11
- [75] Latif A, Kapoor V, Sipra QUAR, Malik SU, Bilal J, Bin Riaz I, et al. Disease milestones through bibliometric analysis of the top 100 cited articles in multiple myeloma. *Cureus*. 2018;**10**(4):e2438. DOI: 10.7759/cureus.2438
- [76] Saika TK. Developments in the field of myeloma in the last decade. *Indian Journal of Hematology and Blood Transfusion*. 2017;**33**(1):3-7. DOI: 10.1007/s12288-017-0777-0. Epub 2017 Jan 17
- [77] Munshi NC, Anderson KC. New strategies in the treatment of multiple myeloma. *Clinical Cancer Research*. 2013;**19**(13):3337-3344. DOI: 10.1158/1078-0432.CCR-12-1881. Epub 2013 Mar 20
- [78] Anderson KC. Vision statement for multiple myeloma: Future directions. *Cancer Treatment and Research*. 2016;**169**:15-22. DOI: 10.1007/978-3-319-40320-5_2
- [79] Fonseca R, Abouzaid S, Bonafede M, Cai Q, Parikh K, Cosler L, et al. Trends in overall survival and costs of multiple myeloma, 2000-2014. *Leukemia*. 2017;**31**(9):1915-1921. DOI: 10.1038/leu.2016.380. Epub 2016 Dec 23
- [80] deSouza JA, Muffly L. The overlooked cost of multiple myeloma. *The Lancet Haematology*. 2015;**2**(10):e394-e395. DOI: 10.1016/S2352-3026(15)00192-1. Epub 2015 Sep 17
- [81] Yamabe K, Inoue S, Hiroshima C. Epidemiology and burden of multiple myeloma in Japan: A systematic review. *Value in Health*. 2015;**18**(7):A449. DOI: 10.1016/j.jval.2015.09.1129. Epub 2015 Oct 20