Chapter

Treatment Approaches of Multiple Myeloma

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Abstract

Multiple Myeloma (MM) is the most common malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. Clinical investigation of MM requires the evaluation of bone marrow for plasma cell infiltration, and detection and quantification of monoclonal protein in the serum or urine, and evidence for end-organ damage (i.e., hypercalcemia, renal insufficiency, anemia, or bone lesions). The overall goal of treatment of MM is to improve survival. The treatment landscape and clinical outcome of MM have changed in the last two decades, with an improved median survival of 8–10 years. Management of MM involves induction, consolidation, and maintenance therapy. Currently, Autologous stem cell transplant (ASCT) is considered as the standard care of treatment for newly diagnosed fit MM patients. Multiple combinations of proteasome inhibitors (PIs) and immunomodulatory drugs (IMIDs) such as Thalidomide, lenalidomide, and pomalidomide have been under evaluation in ASCT-eligible and ineligible settings, and studies are still ongoing. For patients with ASCT-eligible newly diagnosed MM, induction therapy with triple drugs should contain an IMiD, a PI, and a corticosteroid, usually lenalidomide-bortezomib-dexamethasone. For ASCT-ineligible patients on lenalidomide with dexamethasone (Rd), with addition of bortezomib or daratumumab can be considered.

Keywords: Pharmacotherapy of Multiple Myeloma, Standard Treatment of Multiple Myeloma, Advances in Management of Multiple Myeloma

1. Introduction

Multiple Myeloma (MM) is the most common type of plasma cells cancer that mount up from bone marrows, and leads to osteodysfunction and marrow failure [1, 2]. It is second to non-Hodgkin lymphoma as the most common hematologic malignancy [3]. Majority of the MM patients who develop Monoclonal Gammopathy of Undetermined Significance (MGUS) are initially pass through the stage of asymptomatic pre-malignancy [4, 5]. The conversion of MGUS to MM is around 1% per annum, and the more advanced form of pre-malignant stage termed as Smoldering (or indolent) MM (SMM) can also be seen in some patients, that has a progression rate of 10% per annum over the first 5 years of diagnosis, 3% per year over the following 5 years, and 1.5% per year thereafter [4–6].

The European Myeloma Network (EMN) provides recommendations for the management of the most common complications of MM. The whole body low-dose

computed tomography (LDCT) is now considered as novel in detecting lytic lesions, and more sensitive than conventional radiography in depicting osteolytic disease as per the recommendations of the EMN [7, 8].

The treatment landscape and clinical outcome of MM have changed in the last two decades, with an improved median survival of 8–10 years [9]. The initial impact seen with the introduction of three drugs, thalidomide, bortezomib, and lenalidomide [10]. Multiple combinations of proteasome inhibitors (PIs) like bortezomib, carfilzomib, and ixazomib; immunomodulatory drugs (IMIDs) such as Thalidomide, lenalidomide, and pomalidomide; corticosteroids (Cs) such as dexamethasone, prednisone; monoclonal antibodies (MAs) like Daratumumab and isatuximab; and alkylating agents such as melphalan, cyclophosphamide have been tried and evaluated in the transplant and non-transplant settings, and studies are still ongoing [9]. The approval of carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab by the Food and Drug Administration (FDA) for the treatment of relapsed multiple myeloma, in the last five years is an step closer to radical cure [10].

2. Diagnosis

Clinical investigation of MM requires the evaluation of bone marrow for plasma cell infiltration, and detection and quantification of monoclonal protein in the serum or urine, and evidence for end-organ damage (i.e., hypercalcemia, renal insufficiency, anemia, or bone lesions) [11, 12]. This can be done by grouping the different diagnostic and prognostic factors measurable parameters, such as protein analysis, morphology, immunophenotyping, genetics and cytogenetics, and imaging techniques (i.e., MRI, PET/CT) [11].

2.1 Staging in myeloma

According to the International Myeloma Working Group (IMWG) criteria, the diagnosis of MM requires a 10% or more clonal plasma cells infiltration of the bone marrow and/or a biopsy proven plasmacytoma plus any one or more of the myeloma defining events (MDE) which include end-organ damage, characterized by hypercalcemia, renal insufficiency, anemia, or bone lesions which attributable to the underlying plasma-cell disorder; bone marrow clonal plasma cells ≥60%; serum involved to uninvolved free light chain (FLC) ratio ≥ 100 (provided involved FLC level is ≥100 mg/L); or magnetic resonance imaging (MRI) result of more than 1 focal lesion (5 mm or more in size) [10].

2.2 Revised international staging system for myeloma

The following staging is as per the IMWG [13].

1. **Stage I** MM patient will have (all of the following): normal serum lactate dehydrogenase level and without high cytogenetic features; and they will have serum beta-2-microglobulin of <3.5 mg/L and serum albumin level > 3.5 g/dL.

2. **Stage II** patient will have neither stage I or III criteria

3. **Stage III** MM patient will have serum beta-2-microglobulin >5.5 mg/L; and either high risk cytogenetics [t(4;14), t(14;16), or del(17p)] or an elevated serum lactate dehydrogenase level.

Regimen	Usual dosing schedule[a]
Lenalidomide-dexamethasone (Rd)	Lenalidomide 25 mg oral days 1–21 every 28 days Dexamethasone 40 mg oral days 1, 8, 15, 22 every 28 days Repeated every 4 wk
Thalidomide-dexamethasone (Td)[b]	Thalidomide 200 mg oral days 1–28 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Bortezomib-melphalan-prednisone (VMP)[b]	Bortezomib 1.3 mg/m^2 subcutaneous days 1, 8, 15, 22 Melphalan 9 mg/m^2 oral days 1–4 Prednisone 60 mg/m^2 oral days 1 to 4 Repeated every 35 days
Pomalidomide-dexamethasone (Pom/Dex)	Pomalidomide 4 mg days 1–21 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 wk
Bortezomib-Cyclophosphamide-Dexamethasoneb (VCd or CyBord)	Cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15, and 22 Bortezomib 1.3 mg/m^2 subcutaneous on days 1, 8, 15, 22 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks[c]
Bortezomib-thalidomide-dexamethasone (VTd)[b]	Bortezomib 1.3 mg/m^2 subcutaneous days 1, 8, 15, 22 Thalidomide 100–200 mg oral days 1–21 Dexamethasone 20 mg oral on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 4 weeks 3 4 cycles as pretransplant induction therapy
Carfilzomib-Cyclophosphamide-Dexamethasone (KCd)	Carfilzomib 20 mg/m^2 (days 1 and 2 of Cycle 1) and 27 mg/m^2 (subsequent doses) intravenously on days 1, 2, 8, 9, 15, 16 Cyclophosphamide 300 mg/m^2 orally on days 1, 8, 15 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks
Bortezomib-Lenalidomide-Dexamethasone (VRd)[b]	Bortezomib 1.3 mg/m^2 subcutaneous days 1, 8, 15 Lenalidomide 25 mg oral days 1–14 Dexamethasone 20 mg oral on day of and day after bortezomib (or 40 mg days 1, 8, 15, 22) Repeated every 3 weeks[d]
Carfilzomib-Lenalidomide-Dexamethasone (KRd)[e]	Carfilzomib 20 mg/m^2 (days 1 and 2 of Cycle 1) and 27 mg/ m^2 (subsequent doses) intravenously on days 1, 2, 8, 9, 15, 16 Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Carfilzomib-Pomalidomide-Dexamethasone (KPd)[e]	Carfilzomib 20 mg/m^2 (days 1 and 2 of Cycle 1) and 27 mg/ m^2 (subsequent cycles) intravenously on days 1, 2, 8, 9, 15, 16 Pomalidomide 4 mg oral on days 1–21 Dexamethasone 40 mg oral on days on days 1, 8, 15, 22 Repeated every 4 weeks
Daratumumab-Lenalidomide-Dexamethasone (DRd)	Daratumumab 16 mg/ kg intravenously weekly × 8 weeks, and then every 2 weeks for 4 months, and then once monthly Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered) Lenalidomide-Dexamethasone repeated in usual schedule every 4 weeks
Daratumumab-Bortezomib-Dexamethasone (DVd)[b]	Daratumumab 16 mg/ kg intravenously weekly × 8 weeks, and then every 2 weeks for 4 months, and then once monthly Bortezomib 1.3 mg/m^2 subcutaneous on days 1, 8, 15, 22 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered) Bortezomib-Dexamethasone repeated in usual schedule every 4 weeks

Regimen	Usual dosing schedule[a]
Daratumumab-Pomalidomide-Dexamethasone (DPd)	Daratumumab 16 mg/kg intravenously weekly 3 8 weeks, and then every 2 weeks for 4 months, and then once monthly Pomalidomide 4 mg oral on days 1–21 Dexamethasone 40 mg intravenous days 1, 8, 15, 22 (given oral on days when no daratumumab is being administered) Repeated every 4 weeks
Elotuzumab-Lenalidomide-Dexamethasone (ERd)	10 mg/ kg intravenously weekly × 8 weeks, and then every 2 weeks Lenalidomide 25 mg oral days 1–21 Dexamethasone per prescribing information Lenalidomide-Dexamethasone repeated in usual schedule every 4 weeks
Ixazomib-Lenalidomide-Dexamethasone (IRd)	Ixazomib 4 mg oral days 1, 8, 15 Lenalidomide 25 mg oral days 1–21 Dexamethasone 40 mg oral days 1, 8, 15, 22 Repeated every 4 weeks
Panobinostat-Bortezomib[b]	Panobinostat 20 mg oral three times a week 3 2 weeks Bortezomib 1.3 mg/m^2 subcutaneous days 1, 8, 15 Repeated every 3 weeks

[a]All doses need to be adjusted for performance status, renal function, blood counts, and other toxicities.
[b]Doses of dexamethasone and/or bortezomib reduced based on other data showing lower toxicity and similar efficacy with reduced doses; subcutaneous route of administration of bortezomib preferred based on data showing lower toxicity and similar efficacy compared to intravenous administration.
[c]The day 22 dose of all 3 drugs is omitted if counts are low, or after initial response to improve tolerability, or when the regimen is used as maintenance therapy; When used as maintenance therapy for high risk patients, further delays can be instituted between cycles.
[d]Omit day 15 dose if counts are low or when the regimen is used as maintenance therapy; When used as maintenance therapy for high risk patients, lenalidomide dose may be decreased to 10–15 mg per day, and delays can be instituted between cycles as done in total therapy protocols.
[e]Carfilzomib can also considered in a once a week schedule of 70 mg/m^2 on days 1, 8 and 15 every 28 days (cycle 1, day 1 should be 20 mg/m^2); Day 8, 9 doses of carfilzomib can be omitted in maintenance phase of therapy after a good response to improve tolerability; KCd dosing lowered from that used in the initial trial which was conducted in newly diagnosed patients.

Table 1.
Major treatment regimens in multiple myeloma [9, 10].

Different ranges of regimens have been developed to retard progression of disease using potentially effective in controlling and promising for survival. The most commonly used drug combinations are listed in **Table 1**.

2.3 Symptomatic versus asymptomatic myeloma

Urgent management of indolent myeloma is not recommended at the present time; rather treatment should be considered in all symptomatic patients with an active myeloma criteria (the CRAB criteria) (hypercalcaemia >11.0 mg/dl), creatinine >2.0 mg/ml, anemia (Hb < 10 mg/dL), active bone lesions), [9].

3. Goal of treatment

The overall goal of treatment of MM is to improve survival [14, 15]. A complete response (CR) has been observed only in few patients with conventional chemotherapy regimens. The use of high-dose therapy followed by ASCT and the advent of novel therapies, such as thalidomide, lenalidomide, and bortezomib gained much promises [14, 15], and with such treatment many patients are gaining the much needed improvement and CR. Studies reported that the success of CR correlates with

survival, and hence the role of CR as an endpoint in myeloma therapy is becoming prominence. It should also be noted that the benefit of CR is not the same with all treatment regimens [15, 16]. Emerging evidence with novel medications showed that continued treatment has resulted in prolong CR and improved response [16].

4. Management of newly diagnosed cases

Currently, for fit newly diagnosed MM patients (NDMM), autologous stem cell transplant (ASCT) considered as the standard care of treatment. But it should be noted that there is also a remarkable results obtained from the non-transplant setting with novel agent-based treatment, which later raised questions as to the role of upfront versus delayed ASCT [9].

Numerous rescue alternatives that incorporate distinctive combinations of medicines have been developed after the emergence of 2nd generation PIs and IMIDs, monoclonal antibodies (MAs), histone deacetylase inhibitors (HDIs), and, more as of late, check-point inhibitors (CPIs) and small molecules [17, 18]. These promising improvement requests a critical evaluation of treatment options to adequately top up the advantages of different induction, consolidation and maintenance approaches, and to set, a treatment ground so as to compare forthright ASCT, salvage ASCT and allotransplant in the era of novel agent [9].

Several drugs have shown promising activity against MM and are being used in clinical practice [19].

4.1 Induction therapy for ASCT-eligible patients

For patients with ASCT-eligible newly diagnosed MM, induction therapy with triple drugs should contain an IMiD, a PI, and a corticosteroid (Cs), usually lenalidomide-bortezomib-dexamethasone (RVd) [20]. The preferred induction therapy is combination of bortezomib with lenalidomide or thalidomide and dexamethasone (VRd or VTD), as well as the combination of daratumumab with VTD (DaraVTD) [21].

For patients presenting with renal impairment, cyclophophosphamide-bortezomib-dexamethasone is preferred, with the option to switch to RVd up on improvement of renal function. For patients intolerant to the triple therapy, double therapy can be used such as bortezomib-dexamethasone (Vd) and lenalidomide-dexamethasone (Rd), (**Figure 1**) [22].

Induction treatment can be administered for an extended period for up to 6–8 cycles [23]. A third drug can be added up on improvement of the patient started with two drugs. Recent data with carfilzomib-lenalidomide-dexamethasone (KRd) induction has shown much promise, and ongoing studies comparing the upfront KRd versus RVd have shown equivalent outcomes, if not improved [24].

Looking at the options of the novel triple (or quadruple) upfront Vs postpone for NDMM patients, it is widely advised that mobilization, stem cell harvest, conditioning and ASCT should be postponed due to the fear of immunosuppression in the upfront [25]. In patients receiving daratumumab and or lenalidomide-based induction, stem cell harvest without ASCT can be considered so as to achieve an adequate stem cell yield [8]. In this case, Granulocyte colony-stimulating factor (G-CSF) only mobilization with the potential addition of plerifaxor should be considered in order to avoid the immunosuppressive effect of high-dose cyclophosphamide. However, in cases of viral supra-infections like COVID-19, stem cell harvests and any transplant procedures should not be performed within at least 14, and preferably 21, days from the last contact (**Table 1**) [8].

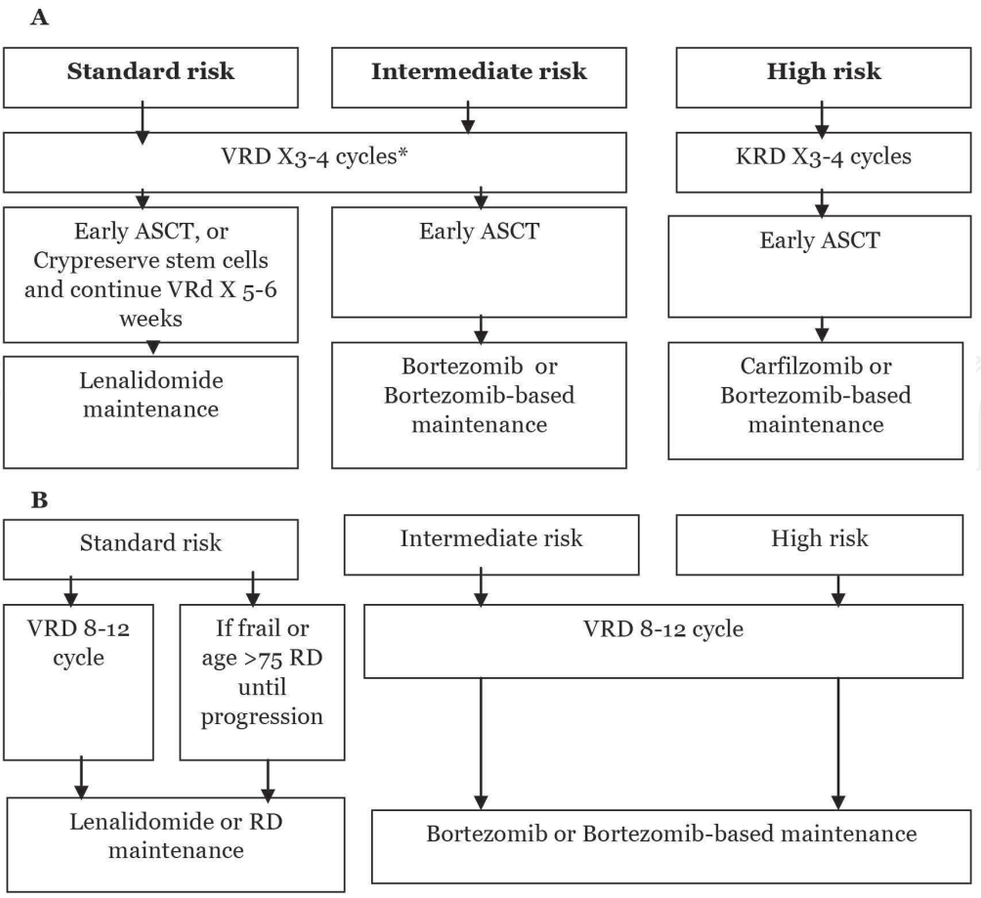

Figure 1.
Approach to the treatment of newly diagnosed multiple myeloma in transplant eligible A, and transplant ineligible B, patients. Abbreviations: ASCT, autologous stem cell transplantation; Dara-VRd, daratumumab, bortezomib, lenalidomide, dexamethasone; DRd, daratumumab, lenalidomide, dexamethasone; VRd, bortezomib, lenalidomide, dexamethasone [10].

The treatment schedule can be modified, for patients with sufficient response. Patients with high-risk disease features may receive ASCT after 6–8 induction cycles due to otherwise increased probability of progression [8]. Quadruple drugs trials are also offering good outcomes and will be available as alternative very soon [26].

4.2 Induction therapy for ASCT-ineligible patients

Patients who are fit or intermediate-fit to Rd. can be put on as a bridge therapy for 2–3 cycles in hospitals with peak prevalence of the current pandemic terror of the COVID-19. Otherwise, the approved VRd or daratumumab-based therapies (DaraRd or DaraVMP) can be administered. Dose of Dexamethasone should be lowered to 20 mg weekly, whereas de-escalation (or even interruption) can be made in patients responding well after the completion of 9 cycles of treatment [8]. Generally, RVd showed an excellent progression-free survival (PFS) and objective response rate (ORR). The triple therapy of daratumumab-lenalidomide-dexamethasone (DRd) showed much improved rates of partial response, better PFS, and tolerance compared to Rd. [27].

4.3 Treatment regimens

Wide ranges of regimens have been developed using a potentially effective combination of drugs that have proven efficacy in controlling disease progression

and improving survival. The most commonly used drug combinations are listed in **Table 1**. The combinations are usually consists of IMIDs, Cs, PIs, and MAs targeting specific cell receptors like CD38, and are playing an important role in the management of MM [28].

Other active agents and approved for the treatment of MM include elotuzumab, a MA that is targeting the signaling lymphocytic activation molecule called SLAMF7 also known as CRACC, CS1, CD319*; panobinostat, a histone deacetylase inhibitor; selinexor, an inhibitor of exportin-1 called XPO1.; anthracyclines, doxorubicin and liposomal doxorubicin. However, elotuzumab, panobinostat, selinexor, and the anthracyclines do not have significant single-drug activity and hence should not be used individually; rather can be used to exert their therapeutic effect in combination with other active agents. Additionally, the anthracyclines are used infrequently in the treatment of MM because of the availability of other more active agents. In aggressive and refractory cases doxorubicin can be incorporated into some multi-agent combinations [19].

* CRACC: The CD2-like receptor-activating cytotoxic cell; CS1: subset 1.

4.4 Treatment algorithm

4.5 Consolidation therapy

The aim of consolidation is to increase the depth of response after induction, because achieving complete response or better is associated with improved survival (**Figure 1**) [16]. Consolidation may consist of ASCT (current standard of care for eligible patients) and/or single or multiple-drug agents after ASCT [29]. In ASCT-ineligible patients, consolidation may consist of single- or multiple-drug regimens [27].

Different types of stem-cell transplantations (SCT) has been used in MM including single ASCT, tandem ASCT, and, rarely, allogeneic stem-cell transplantation (alloSCT)) [30]. A three-arm trial that compared the outcome of RVd induction alone, single ASCT, and tandem ASCT, followed by all on lenalidomide maintenance therapy, unearthed that there was no differences on PFS and OS among all arm and concluded that the single ASCT followed by lenalidomide maintenance therapy has to be continued as the standard of care MM treatment [27].

For all eligible patients, after detail discussion on the outcomes of therapy, upfront ASCT can be used with four cycles of RVd followed by ASCT and four more cycles of RVd. Alternatively, eight cycles of RVd upfront, before ASCT can also be tried. Some patients prefer the latter option, to minimize treatment disruptions in case complications arise because of ASCT. If patients choose to defer upfront ASCT after being informed of the risks and benefits, then collection and storage of stem cells should be begun after four cycles of RVd [31].

4.6 Maintenance therapy

Maintenance therapy improves PFS and OS as compared to therapy cessation, indeed in high-risk patients [29, 32]. The survival benefit is present regardless of whether or not patients receive ASCT before maintenance. The use of maintenance does not seem to lead to decreased efficacy of therapy after first relapse and therefore is standard practice [29].

The IMWG reach on consensus that thalidomide maintenance therapy after ASCT improves the quality of response and increases the PFS as well as the OS significantly [33] though no improvement was seen in OS among elderly patients [33, 34].

Lenalidomide maintenance treatment after ASCT and after conventional melphalan, prednisone, and lenalidomide induction therapy showed a significant risk reduction of PFS as well as improvement in OS. Nevertheless, the role of thalidomide maintenance after induction therapy of melphalan, prednisone, and thalidomide is not yet well established [33].

Compared with conventional induction and thalidomide maintenance treatment a significantly increase in OS was seen with a bortezomib-based induction and bortezomib maintenance therapy after a single-agent bortezomib or in combination with thalidomide or prednisone maintenance therapy [35].

Appropriate therapeutic monitoring has to be taken so as to minimize drug associated toxicities during maintenance therapy. The risks and benefits should also be discussed with patients. Since there is no a single guiding principle reached as a consensus of standard care throughout all health care systems, clinical decisions for individual patients must be balanced with the potential benefits and risks specific management approach [36].

The standard agent for maintenance therapy of MM in U.S.A is lenalidomide, and maintenance therapy with lenalidomide is now favored following induction with or without ASCT because of prolonging response and improving PFS and OS. However, the risks with lenalidomide maintenance such as hematologic and solid secondary primary malignancies has to be given adequate focus [37].

Major trials of maintenance therapy for MM prescribed that all standard-risk patients have be managed with lenalidomide maintenance until improved. For high-risk patients, who are characterized as having either del (17p), t(4;14), or t(14;16), have be managed with dual maintenance comprising of lenalidomide and bortezomib each other week as long as safely endured. For patients with contraindications to bortezomib, ixazomib have to be considered once per weekly in lieu of bortezomib [38]. For very young and elderly patients systematic maintenance therapy is not recommended following induction because of the lack of sufficient data [39].

5. Prognostic factors

Cytogenetic abnormalities such as del(17p), t(14; 16), and t(14; 20) have important prognostic implications. Patients with del(17p), occurs in approximately 10% of newly diagnosed MM and in upwards of 80% in relapsed or refractory MM, are classified as high risk because of shortened OS and PFS [27]. Immunoglobulin heavy-chain translocations associated with the highest risk of poor outcomes include t(4;14) which is present in 5% and t(14;16) in 15% of newly diagnosed MM. Patients with both translocations are considered high risk and experience inferior survival [40].

The prognostic factors of MM is divided into four major parts as: 1) Risk Stratification, which includes Staging of MM, Plasma Cell Labeling index (PCLI), Cytogenetics and Gene Expression Profiling (GEP); 2) Monitoring of Response Tools, which includes Serum-Free Light Chain Assay, serum Heavy/Light Chain (HLC) Assay (Hevylite™), and Advanced Imaging Modalities; 3) Minimal Residual Disease (MRD) Monitoring Methods, which includes Circulating Plasma Cells, MRD Monitoring in General, and the Value of Depth of Response; and 4) Novel Prognostic Markers [41].

6. Management of relapsed and refractory cases

Treatment choice of a relapsed or refractory MM, depends on several parameters including age, the type of comorbidities, performance status, aggressiveness of

relapse, efficacy and tolerance with the previously used medications, the number of prior drugs, the available remaining treatment options, the cytogenetic data at the time of relapse and the interval since the last therapy [27, 42].

Generally, During relapse a triple therapy is preferred over two drug treatment [43]. It should also be noted that, if patients relapse while receiving lenalidomide maintenance, carfilzomib-pomalidomide-dexamethasone and pomalidomide-bortezomib-dexamethasone are options in fit patients [44]. In transplant deferred cases, ASCT may be a good option [44].

For patients who were receiving bortezomib maintenance at the time of relapse or treatment failure, KRd may be used in fit patients. KRd demonstrated improved ORR, PFS, and OS in this population [45].

KRd and DRd may be considered for fit patients not receiving maintenance during relapse [46], and for frail patients or for those with indolent relapse ixazomib-lenalidomide-dexamethasone (IRd) or elotuzumab-lenalidomide-dexamethasone (ERd) may be considered [10, 46].

Pomalidomide-dexamethasone (Pd) is an option for patients with relapsed or refractory MM who have failed lenalidomide and bortezomib, and have received at least two prior therapies [47], the regimen improves PFS and OS in this population. The use of Pd in patients with relapsed or refractory MM who harbor del(17p) showed good prognostic factor [48].

Other combinations for relapsed or refractory MM include daratumumab-pomalidomide-dexamethasone, a PI with panobinostat, carfilzomib-cyclophosphamide-dexamethasone, and pomalidomide-cyclophosphamide-dexamethasone [27, 49].

For frail patients or for those with indolent relapse who relapsed during bortezomib maintenance, DRd, IRd, or ERd are effective [50]. Daratumumab-bortezomib-dexamethasone (DVd) or ixazomib-cyclophosphamide-dexamethasone are also options in frail patients [51].

Data comparing second ASCT to salvage therapy with novel PIs, IMiDs, or monoclonal antibodies not sufficient [17]. In addition, since lenalidomide maintenance is currently the standard of care after ASCT, the goal of considering a second transplantation should be closer to 36 months compared with 18 months on the basis of historical data [52]. If patients relapse after lenalidomide maintenance, considering a pomalidomide-based regimen, such as carfilzomib-pomalidomide-dexamethasone is recommended [27].

7. Supportive therapy

Supportive care is critical throughout the clinical course of patients with MM because they are particularly susceptible to infections. Diligence in identifying and initiating treatment at the earliest sign is advised [27].

All MM patients with newly diagnosed MM and with adequate renal function should be initiated with monthly bone-modulating therapy at diagnosis with either denosumab, zoledronic acid or pamidronate (high recommendation) [27].

Patients with clinical manifestation of MM but without objective evidence of lytic lesions using the conventional radiography can be managed with zoledronic acid (intermediate recommendations), though its advantages using the more advanced objective measurements like CT and MRI is not yet well established [53].

In patients without clinical manifestations of myeloma, the use of bisphonphonates is not generally advised (high evidence of toxicities) [8]. The continuous use of Zoledronic acid recommended as long as the cycles of treatments are on progress, but sufficient data are lacking supporting it after partial response to therapy is

achieved [54, 55]. Denosumab doses can be administered at home if nursing facility is available or the patient should be trained for self-administration. Long-term discontinuation of denosumab treatment is associated with rebound effect and thus should be circumvented [8].

Sufficient data are available that prohibits the use of bortezomib-based regimens in patients with baseline clinical renal impairments. However, evidences are lacking supporting the discontinuation of therapy in patients who develop drug induced renal impairments [56, 57].

Severely anemic patients who do not respond to the conventional anemia management or deteriorating should be urgently switched to erythropoiesis stimulating agents (ESAs) in order to prevent the need for blood transfusions and frequent hospital visits. At present, the whole blood supplies has been extensively restricted due to the COVID-19 lockdown [8]. There are only few data advocating the use of ESAs in patients with persistent symptomatic anemia (hemoglobin <10 g/dL) where other causes of anemia have ruled out. Hence, ESAs should be discontinued after 6–8 weeks of therapy in patients' who fail to respond adequately to anemia treatment [58].

Immunization against influenza is recommended for specific infections caused by streptococcus pneumonia and hemophilus influenza, but sufficient data are lacking supporting the efficacy of the vaccination due to the fact that suboptimal immune responses are fairly seen after management [59].

If patients are receiving PIs & ASCT, the prophylactic use of antiviral agents such as acyclovir (or valacyclovir) are highly recommended [8, 60]. Acyclovir should be prescribed according to local protocols. Immunoglobulin administration may be given in an individualized basis, depending on the depth of suppression of polyclonal immunoglobulins and patient history of recurrent infections [34].

Antiviral prophylaxis has to be recommended in drugs associated with increased risk of herpes zoster reactivation such as Daratumumab and PIs. The prophylaxis is recommended for at least 3 months after exposure if no contraindications are observed [61].

Routine prophylaxis immunization should be considered with a series of pneumococcal conjugate vaccine 13 and pneumococcal polysaccharide vaccine, as well as annual influenza immunization [62]. Drugs such as IMiDs enhance the risk of venous thromboembolism, so preventive measures should be considered during active therapy [61], and the antithrombotic prophylaxis should be considered according to local or international guidelines. For countries with high incidence of COVID-19, low-molecular-weight heparin (LMWH) has to be preferred over aspirin as thromboprophylaxis in MM patients under IMiD administration, irrespective of their thrombotic risk [8, 63].

Patients with a history of neutropenias and/or recurrent infections should receive prophylactic G-CSF injections. Co-trimoxazole prophylaxis for Pneumocystis jirovecii for all patients and levofloxacin prophylaxis for the first three months of treatment for NDMM patients are also highly recommended [8, 55].

8. Follow-up and monitoring

Patients should be followed-up and monitored for complete blood counts (CBC), serum and urine electrophoresis with or without the use of serum-FLC determination, and also for serum calcium and creatinine measurements; at least in 2–3 months interval. In patients are complaining of bone pain, skeletal X-ray, MRI or CT scan should be carried out to detect and rule out new bone lesions [64].

9. Emerging role of targeted therapies, monoclonal antibodies, and cellular therapies

9.1 Venetoclax

Venetoclax is an orally bioavailable selective B-cell lymphoma 2 (Bcl-2) inhibitor. Bcl-2 and cyclin D1 are over expressed in MM patients with a translocation of (11;14), which is present in approximately 20% of patients with MM [65]. Venetoclax is an antiapoptotic protein and an emerging and effective treatment for relapsed or refractory MM [66, 67], and also being tried for treatment of chronic lymphocytic leukemia (CLL) cells [66] and non-Hodgkin lymphoma (NHL) [65]. Although response rates with venetoclax-dexamethasone are impressive in patients with t(11;14), PIs, which inhibit induced myeloid leukemia cell differentiation protein (Mcl-1), have synergistic activity when combined with venetoclax [27].

Currently the venetoclax is suspended by the Food and Drug Administration (FDA) because of a report obtained from the BELLINI trial, which stated an increased relative risk of death in the venetoclax group. As more recent data are being collected to have a better understanding of the safety concerns raised by the BELLINI trial [27, 68].

9.2 BRAF & BRAF/MEK inhibitors

BRAF is a proto-oncogene, that its protein product is a serine/threonine-protein kinase B-Raf that make conform the MAP kinase/ERKs signaling pathway, which works during cell division and differentiation [69]. In patients with MM, the incidence of BRAF V600E mutations is about 7–12% [70]. Trials evaluating BRAF and BRAF/MEK inhibitors in patients with MM harboring BRAF mutations are still undergoing [71].

9.3 Monoclonal antibodies (CAR T cells and BCMA)

Monoclonal antibodies represent an emerging class of agents in MM treatment [72]. Daratumumab-RVd versus RVd, are being evaluated for ASCT-eligible patients [27]. Isatuximab, a humanized immunoglobulin G1 monoclonal antibody, has distinct characteristics in contrast to other anti-CD38 monoclonal antibodies [72]. Isatuximab in combination with IMROZ, isatuximab-RVd in ASCT-ineligible patients with newly diagnosed MM are being studied [72]; and isatuximab-Kd (IKEMA) and isatuximab-Pd (ICARIA) have been tried in patients with relapsed or refractory MM [73].

B-cell maturation antigen (BCMA) is a significant target communicated on MM cells, with other targets counting GPR5CD, CD138, CD74, CD48, CD38, SLAMF7, and transmembrane activator and calcium modulator and cyclophilin ligand (CAML) interactor (TACI). Several strategies targeting BCMA include conjugated antibodies, cellular approaches, and bispecific T-cell engagers. Clinical trials evaluating BCMA-directed Chimeric antigen receptor redirected T cells (CAR-T cells) are furthest in development. Two notable BCMA CAR T-cell products are bb2121 and LCAR-B38M.69–71 Trials are evaluating CAR T cells in patients with relapsed or refractory MM to better understand their role in the MM treatment paradigm [74, 75].

Newly introduced therapies that uses CAR T cells and BCMA antibodies bid promises of adding agents to the antimyeloma armamentarium of neoadjuvant mechanisms of actions [49]. Enduring trials will permit for the integration of

therapies with novel mechanisms of action, with the goal of inducing deeper responses as we endeavor towards the prospect of curative aspect of MM [27].

10. Conclusions

There is no cure for MM until today, however the recent advancements in management approaches provide hope for complete remission with improved survival. ASCT is currently considered the standard of care for fit newly diagnosed MM patients. Multiple combinations of PIs and IMIDs, salvaged with MAs, CTs, and other chemotherapeutic agents have been evaluated and available for both ASCT-eligibles as well as ineligible settings, while further studies are still running.

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Conflict of interest

The authors declare no conflict of interest.

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