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Review

Advancements in Multiple Myeloma Treatment: Insights from Clinical Trials in Asia

Ting Fang Tang [1], Chin Sum Cheong [2], Nur Adila Anuar [2], Won Fen Wong [1,*] and Gin Gin Gan [2,*]

[1] Department of Medical Microbiology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur 50603, Malaysia
[2] Department of Medicine, Faculty of Medicine, Universiti Malaya, Kuala Lumpur 50603, Malaysia
[*] Correspondence: gangg@ummc.edu.my (G.G.G.); wonfen@um.edu.my (W.F.W.)

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Abstract: Multiple myeloma (MM) is one of the most common hematological cancers characterized by the abnormal expansion of clonal plasma cells, resulting in the secretion of abnormal monoclonal proteins and disruption of normal hematopoiesis in human bone marrow. Despite historically lower prevalence than in Western nations, an increasing incidence of MM has been noted in Asian countries. In recent years, the therapeutic landscape of MM has undergone a major transformation with the development of proteasome inhibitors (PIs) and monoclonal antibodies (mAbs), which have now emerged as cornerstones of treatment. PIs such as bortezomib, carfilzomib, and ixazomib selectively inhibit the proteasome, disrupting protein homeostasis in myeloma cells and inducing apoptosis. Bortezomib, the first-in-class PI, revolutionized MM therapy, while second-generation inhibitors like carfilzomib and ixazomib have improved potency and safety profiles. mAbs, including anti-CD38 agents (daratumumab and isatuximab) and the anti-SLAMF7 agent (elotuzumab), have markedly enhanced survival outcomes by specifically attacking myeloma cells and promoting immune-mediated destruction. Daratumumab, in particular, has shown exceptional efficacy both as monotherapy and in combination regimens, leading to its widespread adoption in frontline and relapsed/refractory MM (RRMM) settings. Other emerging therapies such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies are revolutionizing MM management. CAR T-cell therapy, particularly BCMA-targeted constructs, has yielded impressive clinical outcomes in RRMM but is limited by manufacturing challenges, toxicities, and durability of response. Bispecific antibodies, which simultaneously target myeloma cells and T cells, offer promising efficacy. Additionally, newer drug classes, including selective nuclear export inhibitors, histone deacetylase inhibitors, and novel small-molecule inhibitors, are being explored to overcome resistance mechanisms. This review provides a comprehensive overview of MM pathophysiology and disease progression, with a focus on the landscape of treatment strategies in Asian countries.

Keywords: Asia; Clinical Trials; Immunomodulatory Drugs (IMiDs); Multiple Myeloma; Monoclonal Antibodies (mAbs); Proteasome Inhibitors (PIs)

1. Introduction

Multiple myeloma (MM) is a hematologic malignancy marked by the clonal expansion of aberrant plasma cells in the bone marrow. It comprises about 10% of all blood cancers and poses a considerable clinical challenge due to its heterogeneity, resistance to treatment, and high relapse rates. The disease primarily affects older adults, with a median age at diagnosis of 65 to 70 years, and is slightly more prevalent in men. The exact etiology of MM remains unclear, though genetic predisposition, environmental factors, and chronic immune stimulation have been

implicated in its development. Advances in diagnostic techniques and therapeutic interventions have significantly improved survival outcomes, yet MM remains incurable, necessitating ongoing research into novel therapeutic approaches.

1.1. Pathophysiology and Disease Progression of Multiple Myeloma

MM is characterized by the uncontrolled expansion of abnormal plasma cells, leading to excessive secretion of non-functional monoclonal protein (M protein). Plasma cells are terminally differentiated B lymphocytes responsible for producing antibodies, which are essential for humoral immunity. Originating in the bone marrow, naive B cells undergo antigen-specific activation in secondary lymphoid organs such as the spleen and lymph nodes. Upon encountering an antigen, B cells differentiate into plasmablasts, which mature into plasma cells. Under normal conditions, plasma cells produce polyclonal antibodies, ensuring a diverse immune response to pathogens. Five major classes of immunoglobulins (Ig) including IgG, IgA, IgM, IgE, and IgD, each serve distinct immune functions. Most common type of MM involves IgG, followed by IgA. Less frequently, MM can involve IgM, IgD, or IgE. Additionally, some cases present as light chain myeloma, where only free light chains (kappa or lambda) are produced without intact immunoglobulin molecules. Plasma cells typically reside in the bone marrow, where they account for less than 5% of total cells and continuously secrete antibodies under tight regulatory control. Once their function is complete, they undergo apoptosis to prevent excessive antibody production.

In MM, plasma cells escape these regulatory mechanisms, leading to uncontrolled proliferation and excessive monoclonal antibody (M-protein) secretion. This abnormal expansion disrupts normal hematopoiesis, contributing to complications such as anemia, immunosuppression, renal dysfunction, and osteolytic bone disease. The process of oncogenic conversion of normal plasma cells into cancerous myeloma cells is driven by genetic and microenvironmental alterations. Chromosomal translocations involving the *immunoglobulin heavy chain (IgH)* gene on chromosome 14, such as t(4;14), t(14;16), and t(11;14), dysregulate oncogenes like *fibroblast growth factor receptor 3 (FGFR3)*, *multiple myeloma SET domain (MMSET)*, and *v-maf musculoaponeurotic fibrosarcoma oncogene homolog (MAF)*, leading to unchecked proliferation. Additionally, deletion of chromosome 17p, encompassing *TP53 tumor suppressor gene*, is associated with aggressive disease and resistance to standard therapies. As MM progresses, secondary mutations accumulate, further driving clonal evolution and increasing therapy resistance.

Bone marrow microenvironment is pivotal in supporting myeloma cell survival and driving disease progression. Bone marrow stromal cells secrete interleukin-6 (IL-6) and insulin-like growth factor-1 (IGF-1), which promote MM cell proliferation and inhibit apoptosis. Malignant plasma cells also induce angiogenesis through vascular endothelial growth factor (VEGF), supporting tumor growth. Additionally, myeloma cells express adhesion molecules such as very late antigen-4 (VLA-4), which enhance interactions with the bone marrow stroma to foster drug resistance and immune evasion. A hallmark feature of MM is osteolytic bone disease, caused by an imbalance in bone remodeling. MM cells secrete receptor activator of nuclear factor-kappa B ligand (RANKL), which stimulates osteoclast activity, leading to excessive bone resorption.

1.2. Disease Progression and Clinical Presentation

MM follows a stepwise progression from precursor conditions to active disease. Monoclonal gammopathy of undetermined significance (MGUS), is the emergent phase of MM distinguished by minimal M-protein concentration without any signs of organ dysfunction. MGUS progresses to MM at a rate of approximately 1% per year. Some patients develop smoldering multiple myeloma (SMM), an intermediate stage with moderate M-protein levels and an elevated risk of advancing to symptomatic MM. The transition to active MM is marked by the onset of end-organ damage, commonly assessed using the CRAB criteria: hypercalcemia, renal dysfunction, anemia, and bone abnormalities.

The clinical presentation of MM varies depending on disease burden and systemic involvement. Bone pain, particularly in the spine and ribs, is one of the most common symptoms and results from osteolytic lesions and fractures. Anemia, caused by bone marrow infiltration and suppression of erythropoiesis, leads to fatigue, pallor, and weakness. Renal dysfunction, often due to cast nephropathy from excessive free light chains, is a significant complication, contributing to electrolyte imbalances and chronic kidney disease. Hypercalcemia, a consequence of bone resorption, presents with polyuria, constipation, altered mental status, and cardiac arrhythmias. Additionally, immune suppression due to impaired normal immunoglobulin production predisposes patients to recurrent infec-

tions, including bacterial pneumonia and sepsis [1,2]. The diagnosis of MM is established with the detection of ≥ 10% clonal plasma cells in the bone marrow, or a biopsy-confirmed plasmacytoma, accompanied by at least one myeloma-defining event. Laboratory assessments used in assisting MM diagnosis include serum and urine protein electrophoresis, immunofixation, and serum free light chain assays. Bone marrow aspiration and biopsy, combined with flow cytometry and fluorescence in situ hybridization (FISH), facilitate the identification of cytogenetic profile and enable patient risk stratification.

2. Epidemiology and Clinical Characteristics of Multiple Myeloma in Asia

Over the past decades, numerous clinical trials have evaluated emerging treatments with promising outcomes, though the majority have been conducted in Europe and the United States. While these findings are often generalized to Asian populations, pharmacogenetic variations among Asian patients may influence drug metabolism and therapeutic responses, necessitating further region-specific studies [3]. The incidence of MM varies across ethnic groups and geographical regions. For instance, African Americans have a consistently higher propensity of developing MM [4], whereas its incidence in Asia is lower than in Western countries [5,6]. However, despite this historically lower prevalence, East Asian regions, including China and North Korea, have experienced a sharp increase in cases from 1990 to 2016 [7]. In China, the incidence crude annual incidence of newly diagnosed multiple myeloma (NDMM) per was reported at 1.15 per 100,000 person-years in 2016 [8]. Asian patients tend to be identified earlier in life relative to their counterparts. Studies reported a median age of onset of 62 years old among Asian populations, whereas in Western countries, the median age spans between 66 to 70 years [5,9]. The IgG subtype is the most commonly reported type of MM in Asia, accounting for 55.2% of cases. The most frequent clinical manifestation is anemia (60.7%), followed by azotemia (23.4%). The majority of Asian MM patients are diagnosed at advanced stages, with 44.0% presenting at stage III and 36.1% at stage II, according to the International Staging System (ISS) [5].

3. Current Therapeutic Approaches of Multiple Myeloma

MM remains untreatable despite advancement in pharmacological approaches with most patients eventually relapsing and becoming refractory to standard therapies [10,11]. The primary goal of MM treatment is to achieve deep and sustained remission through a combination of induction therapy, autologous stem cell transplantation (ASCT), and maintenance therapy. According to recent guidelines, treatment strategies for NDMM patients involve induction regimens that typically include three or four drug classes, such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), corticosteroids, and monoclonal antibodies (mAbs). Induction therapy aims to reduce tumor burden, control disease progression, and optimize patients for subsequent ASCT, which remains a key treatment component for eligible individuals, particularly younger and fit patients undergoing high-dose chemotherapy. Post-ASCT, maintenance therapy is recommended to prolong remission and delay relapse. The advent of novel therapies has led to a considerable improvement in the prognosis of MM over recent years [7]. Recent advances in biotechnologies have further accelerated the advancement of cutting-edge therapeutic strategies. Novel treatment approaches, including chimeric antigen receptor (CAR) T-cell therapies and bispecific antibodies, are already approved in certain part of the world and studies have demonstrated encouraging efficacy, particularly in relapsed/refractory MM (RRMM) patients. Although these emerging treatments hold promise for achieving greater responses, their long-term impact on survival, adverse effects and overall disease control remains to be fully defined.

4. Clinical Trial Outcomes in Multiple Myeloma Immunotherapy in Asian Countries

In Asia, clinical trials have predominantly been conducted in developed countries such as Japan and South Korea. The clinical landscape of MM has been shaped by various clinical trials evaluating the efficacy and safety of novel therapeutic regimens. While many treatment strategies have been extrapolated from Western clinical studies, pharmacogenetic differences and healthcare disparities necessitate region-specific research. This section reviews the results of major MM clinical trials conducted in Asia, highlighting their impact on treatment efficacy, patient response, and regional treatment disparities. Studies using different drug classes are as tabulated in **Table 1**.

Table 1. List of MM Clinical Trials Employing Immunotherapeutic Approaches in Asia or in Multinational Studies Including Asian Populations.

Drug Classes	Drugs	Descriptions	References
Monoclonal antibodies	Daratumumab (Phase 3 POLLUX)	RRMM patients who received daratumumab with lenalidomide and dexamethasone (DRd) regimen, especially Japanese patients had longer median PFS and sustained treatment response in comparison of lenalidomide and dexamethasone alone (Rd).	[12,13]
	Daratumumab (Phase 3 CASTOR)	RRMM patients receiving daratumumab, bortezomib, and dexamethasone (D-Vd) had improvedmedian PFS and OS (83% vs. 65%) than bortezomib and dexamethasone (Vd) group after median follow-up of 8.2 months. D-Vd benefits patients treated previously with bortezomib and with high-risk cytogenetics.	[14–16]
	Isatuximab (Phase 3 CARIA-MM)	RRMM patients from 24 countries who received isatuximab with pomalidomide-dexamethasone regimen had longer median PFS compared to pomalidomide-dexamethasone group. Isatuximab was proven safe and useful for individuals who develop resistance to lenalidomide and a proteasome inhibitors (PIs).	[17]
	Isatuximab (Phase 1/2)	The ORR in Japanese RRMM patients was 36.4%, the median PFS was 4.7 months, and the median OS not attained during the study period. Isatuximab demonstrated good tolerability and efficacy in patients even in those with high risk cytogenetic.	[18]
	Denosumab (Phase 3 NCT01345019)	Of 196 Asian patients receiving denosumab or zoledronic acid, fewer in the denosumab group developed first on-study skeletal-related events compared with the zoledronic acid group. Among 80 Chinese myeloma bone disease patients, denosumab minimizes nephrotoxicity and has strong antiresorptive effect.	[19,20]
	Belantamab mafodotin (Phase 1 DREAMM-11)	Belantamab mafodotin monotherapy was tolerated among RRMM patients. Combinational therapy of belantamab mafodotin plus bortezomib (or pamalidomdide) and dexamethasone in Japanese individuals show no dose-limiting toxicities.	[21]
	Teclistamab (Phase 1/2 MajesTEC-1 study)	Among 165 patients who received teclistamab, teclistamab resulted in a high frequency of profound and sustained therapeutic responses. Improved PFS was observed in patients with a reduced percentages of T cells expressing exhaustion markers and immunosuppressive regulatory T cells (Tregs).	[22,23]
	Elranatamab (Phase 3 MagnetisMM)	Japanese patients receiving elranatamab monotherapy, ORRs were 50.0% and 58.3% in MagnetisMM-2 and MagnetisMM-3, respectively.	[24]
Immuno-modulatory drugs	Lenalidomide with dexamethasone (Rd) (Phase 3 trial)	The ORR obtained in RRMM patients in Taiwan,China was 34.7% and the median TTP was 20.5 months.	[25]
		The regimen benefited RRMM patients with renal impairment and IgD subtype as well. The ORR was 47.6%, 47.1 % of the recipient maintained disease stability and 5.3% had PD.	[26]
		The ORR obtained from 26 Japanese NDMM patients was 87.5% with 29.2% of them achieved CR/VGPR. The median PFS and OS had not been attained at the time of analysis.	[27]
		From 40 NDMM Japanese patients, the ORR was 68.6% and the 2-year OS rate was 88.5%.	[28]
		Continuous treatment of Rd until disease progression (Rd continuous) reduced the likelihood of disease progression or mortality in comparison with melphalan, prednisone, and thalidomide (MPT) regimen and Rd for 18 cycles (Rd18) regimen. NDMM patients from China and South Korea shared similar effectiveness with patients from other continents.	[29,30]
	Pomalidomide plus dexamethasone (PomDex) plus cyclophosphamide (PomCyDex) (Phase 2 trial)	In 136 Asian RRMM patients, cyclophosphamide was added to the treatment regimen if there is less than a minimal response after 3 cycles of PomDex. Addition of cyclophosphamide improved the median PFS and OS.	[31]
		The ORR, CBR, median PFS, and median OS achieved were 58.2%, 72.7%, 6.9 months and 18.48 months, respectively. 70.8% of the RRMM participants experienced more than grade 3 non-hematological toxicities.	[32]
	Pomalidomide-bortezomib-dexamethasone (PVd) (Phase 3 OPTIMISMM trial)	Among 17 Japanese RRMM patients with a median duration of follow-up of 14.8 months, the patients receiving PVd achieved better median PFS (17.6 months vs. 4.4 months) and ORR (100% vs. 60%) in comparison with patients in bortezomib and dexamethasone (Vd) group. The treatment outcome and safety profile reported in Japanese patients were consistent with overall patient population.	[33]
	Thalidomide and dexamethasone with zoledronic acid (Phase 2 trial)	From 44 NDMM patients from Singapore, India, and South Korea, 88.6% achieved at least a PR. The CR, nCR, and VGPR were 18.2%, 15.9%, 18.2%.	[34]
Chimeric antigen receptor (CAR)-T	BM38 targeting CAR-T cells (Phase 1 trial)	An open-label study involving 74 RRMM patients in China. Grade 3 and above AEs were observed in 60.8% of individuals. ORR was 87.8%, 73.0% of patients achieved CR. With a median PFS of 18.0 months and unreached median OS, the 4-year follow-up results highlighted durable responses and a favorable long-term safety profile.	[35]
		17 Chinese patients were administered CAR-T cells via IV infusion subsequent to lymphodepletion. The ORR was 88.2% with 76.5% of them achieved sCR and 11.8% achieved VGPR.	[36]
		Out of 23 Chinese patients received the treatment, the median PFS was 17.2 months. The ORR was 87% with 52% achieved sCR. BM38 CAR-T cells can be detected in the 62.2% of the patients after 12 months.	[37]

Table 1. *Cont.*

Drug Classes	Drugs	Descriptions	References
	Fully human B cell maturation antigen (BCMA) targeting CAR (Phase 1 CT103A)	18 RRMM Chinese patients including 4 who had previously exposed to murine BCMA CAR, showed 100% ORR, with 72.2% of them achieved CR or sCR.	[38]
	Humanized anti-BCMA CAR-T cells (Phase 1 C-CARo88)	The ORR, sCR, CR, and VGPR of 31 Chinese RRMM patients received the treatment were 96.4%, 46.4%, 10.7%, and 32.1%, respectively. High dose groups with 4.5–6.0 $\times 10^6$ CAR T cells/kg) achieved the highest CR rate.	[39]
	Anti-CD19 and anti-BCMA CAR-T cells (Phase 2 trial)	A study in China showed that the ORR among 21 RRMM patients receiving the treatment was 95 % with sCR, CR, VGPR and PR of 43%, 14%, 24%, and 14%.	[40]
		62 Chinese patients received the treatment and achieved 92 % ORR and 60% of them achieved CR or better. The median PFS was 18.3 months with median follow-up duration of 21.3 months.	[41]
	BCMA-targeting CAR-T cell (Phase 1/2 trial)	28 RRMM and plasma cell leukemia (PCL) patients with RRMM and 2 patients with primary PCL entered the treatment, the ORR and CR were 90% and 43.3%, respectively. The median PFS was 5.2 months and OS was 14.0 months.	[42]
		The ORR and CR achieved by 49 Chinese patients with RRMM were 77% and 47%, respectively. The median PFS and OS were 10 and 29 months respectively. OS of patients with Eastern Cooperative Oncology Group grade 3–4 was worse than the patients with ECOG grade 0–2 (10.5 months vs. not reached).	[43]
	Idecabtagene vicleucel (Phase 2 trial)	A multi-center study involving 128 patients including patients from Japan. The ORR and CR were 73% and 33%, respectively. The median PFS was 8.8 months with median follow-up duration of 13.3 months.	[44]

Complete remission = CR, near complete remission = nCR, stringent complete response = sCR, partial remission = PR, very good partial remission = VGPR, overall survival = OS, progression free survival = PFS, overall response rate = ORR, clinical benefit rate = CBR, time to progression = TTP, progressive disease = PD, adverse effects = AEs.

4.1. Monoclonal Antibodies (mAbs)

Monoclonal antibodies (mAbs) are generated by hybridomas to target soluble growth factors, cell surface proteins, oncogenic pathway components, and molecular elements involved in cell-cell adhesion. These mAbs exert their therapeutic effects through direct cytotoxicity, complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, or by disrupting interactions between target cells and their microenvironment. Among the mAbs approved by the United States Food and Drug Administration (FDA) for MM therapy are daratumumab, isatuximab, and elotuzumab [45]. Daratumumab and isatuximab target CD38, whereas elotuzumab, a humanized IgG1 mAb, targets the Signaling lymphocytic activation molecule family member 7 (SLAMF7) receptor.

Daratumumab is a fully human anti-CD38 IgG1κ monoclonal antibody. It has recently been incorporated into standard-of-care regimens for elderly NDMM patients who are ineligible for transplantation according to the outcomes from phase III ALCYONE (daratumumab with bortezomib, melphalan, and prednisone) and MAIA (daratumumab with lenalidomide and dexamethasone) trials [46]. Both trials included Asian patients, with subgroup analyses from ALCYONE [47], highlighting improved progression-free survival (PFS) with daratumumab treatment [12,48]. COLUMBA study reported that subcutaneous daratumumab was as effective as intravenous daratumumab [49]. Subgroup analyses from the POLLUX study have shown superior treatment outcomes for East Asian patients receiving daratumumab with lenalidomide and dexamethasone (DRd) compared to lenalidomide and dexamethasone (Rd) regimen [12,13]. Isatuximab, is another anti-CD38 drug used in MM therapy. When combined with the proteasome inhibitor, carfilzomib, or the IMiD drug pomalidomide with dexamethasone in RRMM patients, Isatuximab significantly improved PFS, as shown in IKEMA trial with patients from Japan and Korea [50–52].

Elotuzumab, a humanized IgG1 antibody that specificaly targets SLAMF7, a surface protein highly expressed on MM cells, has demonstrated significant clinical benefits. The phase III ELOQUENT-2 trial reported that addition of elotuzumab to lenalidomide and dexamethasone (ERd) regimen can improve PFS and OS in RRMM patients in comparison to lenalidomide and dexamethasone alone [53–55]. Additionally, promising results have been reported for the combination of elotuzumab, pomalidomide, and dexamethasone in previously treated MM patients. Furthermore, phase 1/2 studies conducted in Japan have confirmed the safety and tolerability of isatuximab and elotuzumab when combined with lenalidomide and dexamethasone [18,56].

Beyond the currently approved monoclonal antibodies, several experimental immune-based therapies are being investigated in clinical trials focusing on MM treatment. One notable example is belantamab mafodotin, an antibody-drug conjugate targeting B-cell maturation antigen (BCMA). Phase I DREAM-11 trial exhibited manage-

able safety and promising clinical activity among Japanese patients with RRMM [21]. Additionally, denosumab, an anti–receptor activator of nuclear factor kappa B ligand (anti-RANKL) antibody, can serve as an effective adjunct to standard-of-care treatments for Asian patients with NDMM and lytic bone lesions [19,20]. These advancements underline the growing immunotherapeutic landscape for MM in Asia.

Another promising agent is elranatamab, a BCMA-directed bispecific antibody that has shown efficacy in clinical trials. Study in Japanese patients showed overall response rate (ORR) of 50.0% and 58.3% in MagnetisMM-2 and MagnetisMM-3, respectively [24]. Teclistamab is another similar bispecific antibody that simultaneously targets BCMA and CD3, which has demonstrated positive outcomes in clinical trials, particularly in triple-class-exposed RRMM patients [22, 23]. Besides, talquetamab, an anti-G protein-coupled receptor family C group 5 member D (GPRC5D) bispecific antibody, is also advancing through clinical trials [57]. Despite the potential of these bispecific antibodies, common adverse events, such as cytokine release syndrome and neutropenia, require careful monitoring to ensure patient safety [22–24].

4.2. Immunomodulatory Drug (IMiDs)

Lenalidomide, thalidomide, and pomalidomide are IMiDs that enhance immune responses by interacting with dendritic cells, T cells, natural killer T (NKT) cells, and regulatory T cells [58]. Additionally, IMiDs disrupt the interactions between myeloma cells with bone marrow stromal cells, inhibit angiogenesis, induce cell cycle arrest, suppress cell migration, and promote apoptosis.

Lenalidomide primarily targets cereblon (CRBN), a key component of the E3 ubiquitin ligase complex, inducing the ubiquitin-dependent proteasomal degradation of designated proteins involved in MM pathogenesis. Lenalidomide, approved over a decade ago for relapsed MM, is now widely recognized as a key component of first-line therapy [59,60]. It is used both as maintenance therapy and as part of a regimen incorporating other novel therapeutics agents for NDMM and RRMM patients. In Asia, lenalidomide plus dexamethasone (Rd) has demonstrated efficacy comparable to global outcomes. A study involving Japanese patients with NDMM reported an ORR ranging from 68.6% to 87.5%, with a two-year overall survival (OS) rate of 88.5% [28]. Subgroup analysis from the FIRST trial in Asian patients showed a superior ORR in those receiving continuous Rd compared to patients receiving a limited duration of Rd or those treated with melphalan, prednisone, and thalidomide (MPT), with ORR of 77.8%, 65.8%, and 57.5%, respectively [30]. In China, patients with RRMM treated with Rd achieved an ORR of 47.6%, with a median response duration of 8.8 months [26].

Pomalidomide, a third-generation IMiD, also targeting CRBN, is used for RRMM patients who were non-responsive to lenalidomide [33]. In phase 3 OPTIMISMM trial, pomalidomide, in combination with bortezomib and dexamethasone (PVd), demonstrated greater therapeutic benefit in RRMM patients previously treated with lenalidomide compared to those receiving bortezomib and dexamethasone (Vd) alone [61]. A phase 2 single-arm, open-label study conducted by the Asian Myeloma Network (AMN), which included patients from Singapore, South Korea, Japan, and Hong Kong, reported that addition of cyclophosphamide to pomalidomide and dexamethasone (Pd) enhanced both PFS and OS [31]. Similar findings were reported in another study involving elderly RRMM patients in South Korea [32].

4.3. Chimeric Antigen Receptor (CAR)-Reprogrammed Autologous T cell Treatment

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a promising treatment for various B-cell malignancies, including MM. B-cell maturation antigen (BCMA), which is widely displayed on the membrane of MM cells, has been identified as an ideal target for MM immunotherapy [62]. Following the demonstration of strong efficacy in early-phase clinical trials, significant efforts have been made to develop novel anti-BCMA CAR-T cell therapies [63]. Encouraged by the high response rates observed in initial studies, clinical studies evaluating CAR-T cell approach for MM treatment have rapidly expanded. The LEGEND-2 study, the first-in-human trial of CAR-T cell therapy for RRMM conducted in China, has reported an ORR of 87.8%, with median OS not yet reached, highlighting the potential of this therapeutic approach [35].

5. Other Therapy Approaches for Multiple Myeloma in Asia

Non-immunomodulatory therapeutic approaches to multiple myeloma primarily include proteasome inhibitors, corticosteroids, and other targeted therapies. Autologous stem cell transplantation (ASCT) also plays a significant role in management of MM. **Table 2** shows some of the clinical trials conducted in Asia involving some of these drugs.

Table 2. List of MM Clinical Trials Employing other Drugs in Asia or in Multinational Studies including Asian Populations.

Drug Classes	Drugs and Combinations	Descriptions	References
Proteasome inhibitors	Bortezomib	Among 100 RRMM patients from Taiwan, China, the median OS and TTP were 9.8 and 11.3 months, respectively. Efficacy and tolerability were similar to global population.	[64]
		RRMM patients who relapsed or progressed after ≥6 months since the last dose of their previous bortezomib therapy were given bortezomib retreatment, 33.3% patients achieved CR, 6.7% patients achieved VGPR, and 20.0% patients achieved PR. RRMM patients with plasmacytoma, plasma cell leukemia and light chain escape are not recommended for bortezomib-based salvage therapy due to very poor prognosis.	[65]
		Japanese RRMM patients who were less than 64 years old and achieved PR with the first course of Vd tend to have better OS and PFS.	[66]
		South Korean NDMM patients with early good response to bortezomib combined chemotherapy had better 3 years PFS (55.6%) and 3 years OS (65.3%) compared with patients with poor response which had 18.4% 3 years PFS and 52.9% 3 years OS.	[67]
		Frontline use of bortezomib could prevent early mortality among high-risk ISS patients in Singapore and South Korea.	[68]
	Bortezomib with dexamethasone (Vd)	In 627 MM patients, the median OS, PFS and TTP were 38.3 months, 14.9 months, and 14.9 months, respectively after received Vd treatment but poor prognosis was observed in patients with high expression of aspartate aminotransferase (AST) and lactate dehydrogenase (LDH).	[69]
	Bortezomib with dexamethasone (Vd) and oral Panobinostat (Phase 2 trial)	The group that received 20 mg of Panobinostat twice weekly had the highest ORR while the group that received 10 mg for 3 rounds every week had the least serious Aes but the lowest ORR. 4.8% of the RRMM patients died but none was deemed treatment related.	[70]
	Bortezomib with Hsp90 inhibitor KW-2478 (Phase 1/2 trial)	A study involving RRMM patients from the Philippines found the regimen was well tolerated. ORR was higher in bortezomib-naïve and lenalidomide-naïve patients compared to those pretreated with these drugs.	[71]
	Bortezomib with melphalan and prednisolone (VMP) Carfilzomib with dexamethasone (Kd) (Phase 3 trial)	The CR was 10% in total of 82 Japanese NDMM patients, HLA genotyping could be useful in predict Bortezomib-induced toxicity and treatment efficacy.	[72]
		RRMM patients who received combined treatment of Kd had superior median PFS and ORR compared to those who received Vd.	[73]
	Carfilzomib, dexamethasone, and daratumumab (KdD) (Phase 3 trial)	A better median PFS and ORR were observed in Asian RRMM patients who received one weekly Kd treatment than Asian patients who received twice weekly Kd.	[74]
		The median PFS of KdD group was not reached while the median PFS of Kd group was 15.8 month with median follow-up of 17 months. The rate of grade 3 or higher AEs was higher in KdD group.	[75]
	Carfilzomib or bortezomib with melphalan-prednisone Ixazomib in combination with lenalidomide and dexamethasone (Ird) (Phase 3 trial)	Transplant-ineligible patients with NDMM recruited from several countries including Asian countries China, Japan, South Korea, Singapore, and Turkey. No statistically significant difference between the regimens was detected.	[76]
		65% of ORR was reported in 43 East Asian RRMM patients (Hong Kong, South Korea and Singapore) and 12 % of them had stable disease. The regimen was well tolerated and AEs were generally manageable.	[77]
		Ixazomib-lenalidomide-dexamethasone improved PFS and OS of patients with RRMM compared to lenalidomide-dexamethasone with limited additional toxicity.	[78]
		Phase 1: Among 13 evaluable Japanese RRMM patients, one patient achieved a PR and seven of them had stable disease.	[79]
Nuclear export inhibitors	Selinexor with dexamethasone (Sd) (Phase 2 trial)	82 heavily pre-treated Chinese patients with RRMM were enrolled, the ORR was 29.3% with a median duration of response of 4.7 months. The median OS and PFS were 13.2 and 3.7 months, respectively. There was no pharmacokinetic ethnicity difference between western and Chinese patients.	[80]
	Selinexor with Vd (Phase 3 trial)	A study of 402 RRMM patients, including those from India, found that selinexor with bortezomib and dexamethasone (XVd) improved median PFS over bortezomib and dexamethasone (Vd) in both high-risk (12.91 vs. 8.61 months) and standard-risk (16.62 vs. 9.46 months) groups. Median OS was slightly lower in the high-risk XVd group (22.87 vs. 24.84 months) but not statistically significant.	[81]

Table 2. *Cont.*

Drug Classes	Drugs and Combinations	Descriptions	References
Histone deacetylase (HDAC) inhibitors	Bortezomib with dexamethasone (Vd) and oral Panobinostat (Phase 2 trial)	A randomized study of 248 RRMM patients across 21 countries, including Lebanon, South Korea, Thailand, and Turkey, found that panobinostat with bortezomib and dexamethasone had the highest ORR (65.1%). The 10 mg for 3 rounds every week group had the fewest serious AEs but the lowest ORR (50.6%). Mortality was 4.8%, with no treatment-related deaths.	[70]
		Out of 31 Japanese RRMM patients participated in PANORAMA-1 study, the ORR was 80.6% with the CR + nCR rate of 48.4% and they achieved median PFS of 15.3 months.	[82]

Complete remission = CR, near complete remission = nCR, stringent complete response = sCR, partial remission = PR, very good partial remission = VGPR, overall survival = OS, progression free survival = PFS, overall response rate = ORR, clinical benefit rate = CBR, time to progression = TTP, progressive disease = PD, adverse effects = AEs.

5.1. Proteasome Inhibitors (PIs)

Bortezomib, ixazomib, and carfilzomib are proteasome inhibitors (PIs) that target the ubiquitin-proteasome pathway, a crucial mechanism for degrading regulatory proteins in cell system. Inhibition of proteasome activity disrupts protein homeostasis, leading to apoptosis due to the accumulating misfolded and dysfunctional regulatory proteins in MM cells [83].

Bortezomib is the first proteasome inhibitor that remains a cornerstone in MM treatment, and is widely used in combination regimens [84]. Bortezomib-based combinations have demonstrated superior efficacy compared to melphalan plus prednisone (MP), the historical standard of care for transplant-ineligible MM patients. A study involving 67 Korean patients receiving bortezomib, melphalan, and prednisone (VMP) confirmed its superior efficacy, showing improved PFS and OS [85].

More recently, new generation PIs, such as carfilzomib and ixazomib, have been introduced into practice. The ENDEAVOR trial, which compared carfilzomib plus dexamethasone (Kd) with bortezomib plus dexamethasone (Vd) in RRMM patients, demonstrated superior outcomes for the Kd group, with a longer median OS (47.8 vs. 38.8 months) and a better safety profile across all subgroups [73]. However, the CLARION study did not show a significant improvement in PFS in transplant-ineligible NDMM patients treated with carfilzomib-melphalan-prednisone (KMP) compared to bortezomib-melphalan-prednisone (VMP) [76].

Consistent with the ENDEAVOR trial, carfilzomib has shown a good benefit-risk profile in Asian RRMM patients. The CANDOR trial, which included RRMM patients from Asia, reported better PFS with carfilzomib, daratumumab, and dexamethasone (KdD) compared to Kd alone, with a comparable incidence of adverse events [75]. Additionally, combining carfilzomib with isatuximab in RRMM patients resulted in a higher very good partial response (VGPR) rate (80%) and complete response (CR) rate (44%) in East Asian cohorts [51].

Ixazomib, the first oral PI, was approved by the FDA in 2015 for RRMM in combination with lenalidomide and dexamethasone (IRd) based on findings from the TOURMALINE-MM1 trial [86]. A subsequent study in China replicated these results, demonstrating superior outcomes for IRd compared to Rd [78]. However, a real-world retrospective study in Japan suggested that lenalidomide-refractory patients and those with non-IgG type MM had poorer outcomes with ixazomib-based therapy [87].

5.2. Selective Inhibitor of Nuclear Export (SINEs)

Selinexor is an oral drug that specifically inhibits exportin 1 (XPO1), a nuclear export protein responsible for transporting proteins out of the nucleus. By blocking XPO1, selinexor prevents the export of these critical proteins, leading to their accumulation in the nucleus and subsequent apoptosis of malignant cells. XPO1 is known to be overexpressed in various malignancies, including MM [52]. Selinexor was recently received approval from the FDA for RRMM patients who are refractory to at least one PI, one IMiD, and daratumumab, based on findings from the STORM study [88]. Currently, a phase 1b/2 multi-arm study (STOMP) is evaluating selinexor in combination with different agents, including IMiDs, PIs, and monoclonal antibodies, in RRMM patients. Preliminary results from some combination arms have shown promising efficacy [89]. As selinexor is a novel agent, limited clinical trials have been conducted in Asia. However, a validation study (MARCH) was performed in China using data from the STORM study to meet local regulatory requirements [80]. This study demonstrated clinical benefits in heavily pretreated patients without introducing new adverse effects.

5.3. Histone Deacetylase (HDAC) Inhibitors

Panobinostat is a potent histone deacetylase (HDAC) inhibitor that is involved in regulating gene transcription, cell differentiation, cell cycle progression, and apoptosis [90]. HDAC inhibition leads to DNA damage and upregulation of pro-apoptotic molecules, thereby promoting cell-cycle arrest and apoptotic cell death in malignant cells. Panobinostat has demonstrated efficacy against MM, particularly when combined with bortezomib and dexamethasone (Vd) [91]. In PANORAMA 3 study, which included RRMM patients from 21 countries, including Lebanon, South Korea, Thailand, and Turkey, panobinostat in combination with bortezomib and dexamethasone achieved an ORR of up to 65.1%, depending on the dosage used [70]. In the future, clinical trial using newer HDAC inhibitors such as quisinostat and ricolinostat may offer more targeted epigenetic regulation with fewer side effects.

5.4. Stem Cell Transplantation

Autologous stem cell transplantation (ASCT) has consistently demonstrated improved response rates in MM, leading to complete remissions and prolonged event-free survival [92]. According to an AMN study, patients who received conventional therapy without ASCT had lower OS compared to those who underwent ASCT as part of their first-line treatment [5]. The rate of ASCT procedures varies significantly across different countries in Asia, primarily due to disparities in healthcare infrastructure, access to transplant facilities, and availability of trained specialists [68]. For instance, ASCT rates in South Korea and Japan range from 273 to 407 per 10 million population, whereas in China, India, and Thailand, the rate is considerably lower, ranging from only 1 to 137 per 10 million population [7].

Allogeneic stem cell transplantation (allo-SCT) is another option for younger MM patients [93]. However, its benefits are limited to a specific subgroup of post-ASCT patients, particularly those who have responded well to prior chemotherapy [94]. A retrospective study in Japan found that allo-SCT using a low-intensity preparative regimen comprising fludarabine and melphalan resulted in a high rate of disease recurrence or progression. Further refinement of allo-SCT protocols is necessary to enhance disease eradication and improve long-term outcomes [95].

5.5. Maintenance Therapy

Maintenance therapy is typically recommended following ASCT or induction therapy, as it can prolong relapse-free survival and improve OS. While lenalidomide-based regimens are the standard maintenance approach for post-ASCT patients, bortezomib-based maintenance has shown greater benefits in patients with intermediate- and high-risk disease [2]. A study by Muranushi et al. reported that among 18 post-ASCT patients who received two years of bortezomib maintenance, none experienced disease progression or grade 3/4 [96]. The two-year OS and PF rates were 92.5% and 62.6%, respectively. Similarly, Rajkumar et al. highlighted that maintenance therapy with either lenalidomide alone or in combination with dexamethasone is particularly beneficial for patients who respond well to triplet therapy [97]. A phase 2 study in Japan demonstrated that consolidation with lenalidomide plus low-dose dexamethasone, followed by lenalidomide maintenance after ASCT, significantly improved ORR, with two-year PFS and OS of 76.3% and 92.1%, respectively [98]. Another retrospective study in Japan found that 63% of NDMM patients achieved stringent CR with lenalidomide maintenance post-ASCT [99]. Although lenalidomide remains the recommended maintenance therapy per international guidelines, financial constraints have led some countries to continue using thalidomide as an alternative. A study in Japan demonstrated that thalidomide maintenance post-ASCT was effective in standard-risk NDMM, providing prolonged relapse-free survival [100].

6. Current Challenges and Future Directions in MM Therapy

MM remains an incurable hematologic malignancy due to persistent challenges such as therapeutic resistance, disease relapse, and treatment-related toxicities. Despite significant advancements with PIs, IMiDs, and mAbs, most patients eventually experience relapse, often driven by clonal evolution, tumor heterogeneity, and minimal residual disease (MRD). Addressing these challenges requires a strategic shift toward more precise and durable therapeutic approaches. One of the most pressing challenges in MM management is overcoming therapeutic resistance and disease relapse. The continued evolution of malignant plasma cells allows drug-resistant subpopulations to survive treatment, rendering subsequent therapies less effective. The persistence of MRD, even in patients who achieve

deep clinical responses, highlights the limitations of conventional monitoring techniques. Current methods often fail to detect small numbers of remaining myeloma cells, which can later drive relapse.

Another major hurdle is patient heterogeneity, particularly among elderly and comorbid populations, who often struggle to tolerate aggressive treatment regimens. Although high-dose chemotherapy and ASCT remain the standard of care for eligible patients, many individuals are unable to undergo such intensive therapies. The balance between maximizing efficacy and minimizing toxicity remains a critical consideration, underscoring the need for more personalized, risk-adapted treatment strategies. In addition to patient-related factors, treatment toxicity and adverse effects pose significant obstacles. Standard MM therapies are associated with side effects such as immunosuppression, neuropathy, and bone-related complications, which negatively affect patients' living standard. PIs such as bortezomib and carfilzomib are commonly associated with peripheral neuropathy, cardiovascular complications, and gastrointestinal issues, while IMiD drugs like lenalidomide and pomalidomide increase the risk of thromboembolism, myelosuppression, and secondary malignancies. mAbs targeting CD38 (e.g., daratumumab, isatuximab) and SLAMF7 (e.g., elotuzumab) can lead to infusion-related reactions and immunosuppression, increasing susceptibility to infections. The advent of CAR-T cell therapy and bispecific antibodies has introduced novel toxicities including cytokine release syndrome, neurotoxicity, and prolonged cytopenias, and infections necessitating close monitoring and early intervention. Given these challenges, optimizing supportive care strategies, including thromboprophylaxis, antimicrobial prophylaxis, and dose modifications, is essential for improving therapeutic adherence and patients' life.

As the landscape of MM treatment evolves, immunotherapy become a paradigm-shifting strategy to overcome resistance and enhance outcomes. mAbs, CAR-T cell therapy and bispecific antibodies represent promising immunotherapeutic approaches to directly eliminate myeloma cells. Beyond immunotherapy, advances in next-gene ration PIs, nuclear export inhibitors, and epigenetic modulators are offering avenues to disrupt myeloma cell survival. Combination regimens incorporating these agents are being explored to enhance their effectiveness and prevent resistance. Improved bone disease management with agents such as denosumab, better infection prevention strategies, and optimized toxicity mitigation measures are essential to ensuring that patients not only survive longer but also maintain functional independence. Moreover, deeper understanding of the MM microenvironment and its interactions with immune cells and stromal components is expected to unlock new therapeutic targets and strategies for disrupting disease progression.

Moving forward, big data and artificial intelligence (AI) are poised to revolutionize MM diagnosis, prognosis, and treatment optimization by integrating vast datasets from genomics, proteomics, imaging, and electronic health records. Additionally, comparative data analysis between Asian countries and other continents may provide deeper insights into regional genetic variations, treatment responses, and healthcare disparities, facilitating more precise and personalized MM management worldwide.

7. Conclusions

In conclusion, this review highlights recent advancements in the treatment landscape for MM, including the introduction of next-generation novel agents. Clinical trial data indicate no significant differences in treatment outcomes between Asian and non-Asian MM patients. However, it should be emphasized that most clinical trials conducted in Asia have been limited to developed nations such as Japan and South Korea. As a result, access to novel MM treatments remains limited in other Asian countries, particularly in regions with the highest unmet medical need. Given the rising incidence of MM in Asia, expanding clinical trial sites to underrepresented countries could help improve access to innovative therapies and enhance treatment outcomes for a broader patient population.

Author Contributions

Conceptualization, N.A.A. and G.G.G; methodology, T.F.T.; writing—original draft preparation, T.F.T.; writing—review and editing, C.S.C., W.F.W. and G.G.G; supervision, G.G.G.; funding acquisition, N.A.A. and W.F.W. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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