Chapter 1
The Role of Targeted Therapy in Multiple Myeloma

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Abstract Targeted therapies are the cornerstone of the treatment of all stages of multiple myeloma (MM), from newly diagnosed to relapsed/refractory myeloma (RRMM). The advent of targeted therapies has improved the overall survival for MM patients compared to conventional cytotoxic therapies alone. Despite increasing response rates, deeper depths of response, and prolonged survival, MM remains incurable. Almost all patients with MM eventually relapse, suggesting the presence of residual clones that are resistant to therapy. This review series explores the available evidence and literature on previous, current, and emerging therapies in MM, as well as the mechanisms of resistance to these therapies. A deeper understanding of these resistance mechanisms will be necessary for the development of improved treatments, potentially reaching a cure for MM.

Targeted therapies are widely incorporated into treatment strategies across the scope of MM including incorporation into induction regimens for transplant-eligible patients. For transplant-ineligible patients, combination therapies including targeted agents are used with the aim to prolong disease free progression. In the setting of RRMM, targeted therapies have become the backbone of treatment in combination with chemotherapy. This chapter will review the history and classes of targeted therapies as well as recent therapies still under trial.

Keywords Multiple myeloma · Targeted therapy · Treatment resistance · Immunomodulatory imide drugs · Proteasome inhibitors · Monoclonal antibody treatment · Histone deacetylase inhibitors

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Abbreviations

BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
ECOG	Eastern Cooperative Oncology Group
Fc	Fragment crystallizable
FDA	US Food and Drug Administration
FISH	Fluorescence in situ hybridization
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
IgG1	Immunoglobulin G1
IL-6	Interleukin-6
IMiD	Immunomodulatory imide drug
IMWG	International Myeloma Working Group
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MoAb	Monoclonal antibody
NK	Natural killer
ORR	Overall response rate
OS	Overall survival
PFS	Progression free survival
PI	Proteasome inhibitor
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
RRMM	Relapsed/refractory multiple myeloma
SLAMF7	Signaling lymphocytic activation molecule F7
SWOG	Southwest Oncology Group
VAD	Vincristine, doxorubicin, and dexamethasone
VEGF	Vascular endothelial growth factor
XPO1	Exportin 1

1.1 Multiple Myeloma Overview

Multiple myeloma is the malignant proliferation of plasma cells derived from a single clone. It accounts for approximately 1% of neoplastic disease and 13% of all hematologic cancers [1]. Multiple myeloma usually evolves from an asymptomatic premalignant stage of clonal plasma cell proliferation—known as monoclonal gammopathy of undetermined significance (MGUS) that progresses to smoldering (asymptomatic) MM and finally to symptomatic MM [1]. Commonly, MGUS may progress to MM or related malignancy at a rate of 1% per year [2]. The annual incidence of MM in the US is 4–5 per 100,000. With advancements in treatment options, the 5-year survival has steadily increased in the last decade and is currently 49%.

In MM, there are important prognostic factors which stratify patients into high and standard risks. These factors include cytogenetic abnormalities deletion 17p or immunoglobulin heavy chain translocations t(4;14) or t(14;16) detected by interphase FISH (fluorescence in situ hybridization). The median overall survival (OS) of patients with high-risk disease is only 2–3 years even with tandem stem cell transplantation compared to >7–10 years in those with standard risk disease [3].

Multiple myeloma displays a complicated karyotype and high levels of genomic instability associated with various gene mutations and chromosomal translocations [4]. Elevated aberrant homologous recombination in myeloma cells is one of the main contributing mechanisms to this instability, resulting in loss of cell cycle control and apoptosis and thus increased disease aggressiveness and treatment resistance [4]. Many studies over the years have demonstrated that MM has complex genetic features. At the chromosome level, MM can be classified into hyperdiploid (48–74 chromosomes) and non-hyperdiploid (common in MGUS) although currently there are no known triggers leading to change in ploidy [5]. There are also various chromosomal gains and losses with no known triggers for chromosomal changes. Furthermore, translocation rearrangements can occur within the immunoglobulin heavy chain gene which can be seen in MGUS and acts as a potential trigger for transformation to MM. Genetic mutations can also affect cell signaling pathways such as RAS, which is one of the most commonly mutated pathways in MM. Due to the capability of various and complex genetic and molecular abnormalities, MM is a very genetically heterogeneous disease.

Currently, there is no strong evidence that early treatment of patients with smoldering MM prolongs survival. However, there are ongoing clinical trials to determine whether targeted agents can delay progression and improve survival in smoldering MM. In transplant-eligible patients with standard risk disease, the current recommendation is induction with triple therapy, with one or two targeted agents followed by stem cell transplant. In patients with high-risk disease, the recommendation is initial treatment with proteasome inhibitor-containing therapy with consideration of clinical trials given that high-risk disease does not respond well to conventional therapy.

The introduction of novel agents has dramatically improved outcomes for MM patients. However, there is no established curative therapy and consequently patients will relapse and eventually develop refractory disease with a limited duration of response to subsequent lines of treatment. The choice of salvage therapy is affected by several considerations including initial therapy, degree, and duration of response to primary therapy, age, performance status, and previous toxicities. Novel agents including proteasome inhibitors (PI) and immunomodulatory imide drugs (IMiD) are currently part of the treatment paradigm.

1.2 Historical Treatment of Multiple Myeloma Until Present

There have been substantial changes in drug design and treatment regimens which have transformed MM from an acute to a chronic condition. With the advent of novel agents introduced as first-line therapy, the 5-year survival rate has been reported to be as high as 80% [6]. A review of the historical treatments for MM demonstrates both the significant changes over the last century and continuing development of new agents.

The first documented case of MM was in 1844 with the first treatment consisting of rhubarb and orange peel mixture with the application of leeches as "maintenance therapy" [2]. In 1947, Alwall reported that urethane reduced serum globulin and decreased bone marrow plasma cells [2]. This was proven to be ineffective as demonstrated in a small trial by Holland [7] in 1966 whereby 83 patients were randomized to either urethane or placebo and no differences in objective improvement or survival were observed.

From 1958 to 1962, Blokhin reported significant improvement in MM patients treated with melphalan [8]. This was followed by Hoogstraten [2] who found that a melphalan loading dose followed by maintenance therapy achieved a response in approximately 78% of patients with either newly diagnosed or previously treated MM [9].

In 1962, Maas was the first to test corticosteroids in MM. At the time, prednisone was trialed as a single agent; however, no difference in survival was observed. The first regimen of melphalan and prednisone was established after Alexanian et al. completed a randomized trial with 183 multiple myeloma patients [10]. This study observed that patients receiving combination regimen had a 6 months longer survival compared to melphalan alone [10]. Pulsed corticosteroids have been an important backbone of myeloma therapy until now [11]. The combination of multiple alkylating agents is efficacious in MM. For example, the M-2 protocol, consisting of carmustine, melphalan, cyclophosphamide, and prednisone resulted in response rates of up to 87% were observed in some groups of patients [12]. Triple therapy of vincristine, doxorubicin, and dexamethasone (VAD) was the main treatment for about 2 decades as induction therapy in newly diagnosed and RRMM [13, 14].

Autologous stem cell transplantation has been a standard first-line therapy for patients who can tolerate the intensity of high dose chemotherapy, due to its impact on survival advantage [15]. This procedure consists of induction chemotherapy, followed by autologous stem cell harvest, high dose melphalan chemotherapy, and reinfusion of harvested stem cells. Prior to the advent of target therapy, induction therapy/chemotherapies included dexamethasone [16], VAD and VAD with dexamethasone, cyclophosphamide, etoposide, and cisplatin [14, 17, 18]. However, the incorporation of novel targeted agents into induction regimens was proven to be superior to conventional cytotoxic chemotherapy like VAD [19]. Hence, the current standard of care involves targeted therapy in the induction phase followed by autologous stem cell transplant.

Maintenance therapy post autologous stem cell transplantation or other induction therapy is important in prolonging the duration of remission and possibly overall survival. Maintenance therapy has evolved over the years from corticosteroids and interferon to novel targeted therapies such as thalidomide, lenalidomide, and bortezomib.

The first targeted agent used in myeloma therapy was thalidomide, an IMiD. An Eastern Cooperative Oncology Group (ECOG) randomized trial demonstrated that the thalidomide-dexamethasone combination was superior to dexamethasone alone as an induction regimen for newly diagnosed MM [20]. This led to the accelerated approval for thalidomide-dexamethasone in 2006 by the US Food and Drug Administration (FDA) for the treatment of newly diagnosed MM. For transplant-ineligible patients, melphalan, prednisone, and thalidomide demonstrated higher response and progression free survival (PFS) when compared with standard melphalan and prednisone [21].

The next targeted therapy utilized in MM was bortezomib, the first PI with significant survival benefit in both transplant-eligible and ineligible MM patients [19, 22]. The combination of melphalan, prednisone, and bortezomib in patients older than 65 years of age has achieved an associated response rate of 89% and increased PFS [23]. Thereafter, there has been ongoing development in subsequent generations of IMiDs and PIs with the aim to further improve overall survival and side effect profiles.

Despite the ongoing development of IMiDs and PIs, resistance to these agents does occur in RRMM. This has led to the development of other agents including monoclonal antibodies (MoAb) such as daratumumab, which have demonstrated rapid and deep responses when used as monotherapy [24] and in combination with bortezomib, lenalidomide, and pomalidomide [25–29].

Histone deacetylase inhibitors (HDACi) target the deacetylation of histones and nonhistone proteins and have synergistic activity with other target therapies. Panobinostat is a pan-HDACi which targets the protein degradation pathway, aggrephagy, and has synergistic activity with bortezomib in MM.

Immunotherapy including chimeric antigen receptor (CAR) T cell therapies and bispecific T cell and natural killer (NK) antibodies are currently being tested in clinical trials. In CAR T cell therapy, T cells are engineered to target specific antigens on myeloma cells such as CD38 or B cell maturation antigen (BCMA). Bispecific antibodies have two targets, engaging T cells or NK cells and specific antigens on the myeloma cells, bringing the myeloma cells in close proximity to activated T cells or NK cells which cause the demise of the myeloma cells.

The outcomes of MM have improved substantially over the past 20 years with the introduction of PIs and IMiDs. These agents, either in triplets or doublets, form the backbone of therapy for MM.

1.3 Immunomodulatory Imide Drugs

Immunomodulatory imide drugs were the first targeted therapy in MM. As a class, IMiDs have a wide spectrum of mechanisms of action including augmentation of NK cells, alterations in cytokine production and T cell activity, and decreasing vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6) expression which inhibits angiogenesis. The introduction of IMiDs into induction regimens has been observed to increase rates of complete response.

Thalidomide was the first IMiD introduced in 1957. Although initially introduced as a sedative and treatment for morning sickness in pregnancy, severe teratogenic malformations were associated with thalidomide use and was subsequently removed from most markets globally by the end of 1961. In certain conditions, thalidomide continued to be used as a therapeutic agent and was approved for the treatment of erythema nodosum leprosum in 1998 [30]. In 1994, thalidomide was found to have significant antiangiogenic properties [31]. Subsequently, in 1997 Barlogie et al. initiated a compassionate-use trial of thalidomide as antiangiogenic therapy [32]. At the time, 84 patients were enrolled with 32% responding to single agent thalidomide [32]. Response rates in newly diagnosed and RRMM were 63% and 50%, respectively when combined with dexamethasone [20, 33]. The response rate of the three-drug combination of thalidomide, steroids, and cyclophosphamide ranged from 60% in RRMM to 80% in newly diagnosed MM [34–36].

Due to the significant neurotoxicity of thalidomide that commonly results in therapy cessation, the second- and third-generation IMiDs, lenalidomide, and pomalidomide, respectively, were developed. Lenalidomide is a derivative of thalidomide, interfering with multiple signaling and survival pathways within myeloma cells and the bone marrow microenvironment. It is more potent than thalidomide but has significantly less neurotoxicity. The FIRST trial demonstrated better median PFS and trends towards better OS when lenalidomide and dexamethasone were used in an upfront setting for transplant-ineligible patients with PFS of 22.5 months, compared to 21.2 months in the melphalan, prednisone, and thalidomide group [37]. This led to its approval in 2015 by the FDA for use as first-line therapy in transplant-ineligible patients. Lenalidomide was also studied in RRMM, with the MM-009 trial demonstrating an improvement in median time of progression (11.1 months in the lenalidomide group compared to 4.7 months in the placebo group) with complete, near-complete, or partial response rates of 60.2% in the lenalidomide group compared to 24% in the placebo group [38].

Pomalidomide is the third-generation IMiD that is chemically related to both thalidomide and lenalidomide but is more active and potent. Currently, pomalidomide is approved by the FDA for third-line treatment in patients with relapsed or progressive MM who have received at least two prior therapies, including lenalidomide and bortezomib. This is based on its significant improvement in PFS and OS in this group of MM patients.

1.4 Proteasome Inhibitors

Proteasome inhibitors were developed following an increased understanding of the role of the ubiquitin-proteasome pathway in MM. This pathway is responsible for the degradation of misfolded and unfolded intracellular proteins. Proteasome inhibition leads to the accumulation of these unfolded or misfolded proteins that induce stress in the endoplasmic reticulum and ultimately apoptosis [39, 40]. Bortezomib is the first in-class PI developed and used for the treatment of MM and acts through multiple mechanisms to suppress tumor survival pathways and arrest tumor growth, spread, and angiogenesis [40]. Preclinical studies demonstrated that bortezomib had potent cytotoxic and growth inhibitory effects on myeloma cells [41]. An open-label phase II study of bortezomib in 202 patients with RRMM and who had failed two prior lines of therapy observed an overall response rate (ORR) of 28% [42]. This led to FDA approval in 2004 for bortezomib to be used as a single agent for the treatment of RRMM. Many randomized studies including the MM5 German study demonstrated the efficacy of bortezomib combined with cyclophosphamide and dexamethasone in untreated MM patients, resulting in lower rates of disease progression and high response rates. Bortezomib has also been used as induction therapy for both transplant-eligible and transplant-ineligible patients [43, 44]. The Southwest Oncology Group (SWOG) S0777 trial demonstrated that combining a PI with an IMiD (bortezomib combined with lenalidomide and dexamethasone) improves OS and PFS compared to the conventional regimen of lenalidomide and dexamethasone [45]. Bortezomib has also been investigated as a potential posttransplantation maintenance therapy. There is evidence that bortezomib-based maintenance may increase response rates and prolong PFS [46, 47].

Despite its efficacy, resistance to bortezomib in MM is inevitable. The mechanism of resistance is heterogeneous and is difficult to predict. The potential resistance mechanisms studied so far include mutations in the β5-subunit of the proteasome, derangement of stress responses, increased proteasomes and survival, and anti-apoptotic pathways [48–52]. In response to developing resistance, the second-generation PI carfilzomib was developed and approved for the treatment of RRMM.

Carfilzomib is indicated for RRMM after at least one previous therapy. It is an epoxyketone-based, irreversible PI that binds the chymotrypsin catalytic site within the β5-subunit of the 20S proteasome. Carfilzomib is active against bortezomib-resistant myeloma cells. It induces extrinsic and intrinsic apoptosis and activates stress response pathways in human MM [53]. In the ASPIRE trial, carfilzomib, lenalidomide, and dexamethasone were compared with lenalidomide and dexamethasone. A longer PFS was observed in the carfilzomib group [54]. Carfilzomib is also superior to bortezomib in RRMM with improved response rates and PFS [55].

Ixazomib is an oral, selective, and reversible PI. It preferentially binds and inhibits the chymotrypsin-like activity of the β5-subunit of the 20S proteasome [56]. Ixazomib demonstrated in vitro cytotoxicity against primary myeloma cells from patients who had relapsed after multiple prior therapies including bortezomib,

lenalidomide, and dexamethasone. Ixazomib in combination with a regimen of lenalidomide and dexamethasone was shown to result in a significantly longer median PFS of 20.6 months when compared to 14.7 months with lenalidomide and dexamethasone, with a hazard ratio of 0.74 [57].

1.5 Monoclonal Antibodies

Monoclonal antibodies were developed to target specific antigens and pathways driving MM. Current MoAbs available for treatment are daratumumab and elotuzumab, both of which are approved for RRMM.

Daratumumab is a human MoAb that targets the highly expressed CD38 glycoprotein on MM cells [58, 59]. It is generated by immunized transgenic mice. Daratumumab is approved for use in combination with lenalidomide and dexamethasone, or with bortezomib and dexamethasone, for the treatment of patients with MM and who have received at least one prior therapy [60]. Approval for the use of daratumumab was based on two randomized clinical trials where the addition of daratumumab to lenalidomide and dexamethasone (POLLUX), and to bortezomib and dexamethasone (CASTOR) improved the 12-month PFS significantly; 83.2% in the daratumumab group versus 60.1% in the control group in the POLLUX trial, and 60.7% in the daratumumab group versus 29% in the control group in the CASTOR trial [29, 61]. Daratumumab has also been found to improve PFS when combined with carfilzomib and dexamethasone in RRMM (CANDOR study).

Isatuximab is a chimeric immunoglobulin G1 (IgG1) kappa anti-CD38 MoAb which is generated by immunized wild type mice [59]. ICARIA-MM43, a multicenter, multinational, randomized, open-label phase III study comparing isatuximab, pomalidomide, and low-dose dexamethasone against pomalidomide and low-dose dexamethasone showed a 40% reduction in risk of disease progression or death with the addition of isatuximab [62]. This led to the FDA approval of isatuximab for use in RRMM.

Elotuzumab is a humanized IgG1 immunostimulatory MoAb targeted against the signaling lymphocytic activation molecule F7 (SLAMF7), a glycoprotein expressed on myeloma cells and NK cells [63]. Expression of SLAMF7 is nearly universal in MM irrespective of cytogenetic abnormalities and disease progression. Elotuzumab exerts a dual effect by directly activating NK cells and mediating antibody-dependent, cell-mediated cytotoxicity through the CD16 pathway [64]. As a single agent, elotuzumab has little clinical activity; however, when combined with lenalidomide and dexamethasone, it reduced the risk of progression or death by 30% with a median PFS of 19.4 months [63, 65]. Elotuzumab attained FDA approval in 2015 for use in the treatment of RRMM.

1.6 Histone Deacetylase Inhibitors

Histone deacetylase inhibitors (HDACi) acetylate histones and nonhistone proteins. The hyperacetylation of histones can reverse the silencing of specific genes. Moreover, hyperacetylation of nonhistone proteins affects their cellular function. Currently, panobinostat is the only HDACi approved for the treatment of relapsed myeloma. Panobinostat, bortezomib, and dexamethasone have been reevaluated as a third-line therapy in MM patients with improvement in PFS when compared to bortezomib and dexamethasone (11.99 months versus 8.08 months), leading to accelerated FDA approval in 2015 [66].

Despite these survival benefits, panobinostat has significant toxicity including diarrhea and cardiac events such as arrhythmias [66]. As such, selective HDACIs are being developed. Ricolinostat is a selective HDAC6 inhibitor which inhibits autophagic protein degradation. In a phase I/II trial, promising results were shown in RRMM when ricolinostat was combined with bortezomib and dexamethasone, with ongoing phase I/II trials further investigating other combinations including ricolinostat with lenalidomide and pomalidomide [67].

1.7 Bone Targeted Therapy

Bone targeted therapy is important in MM as it reduces skeletal lesions and has antitumor effects. Multiple myeloma is characterized by osteolytic lesions, osteopenia, tumor-induced hypercalcemia, and skeletal complications such as pathologic fractures in the long bones or vertebral collapses. Skeletal complications are a major cause of morbidity and mortality.

Targeted agents such as IMiDs and PIs have some direct effects on bone remodeling. Immunomodulatory imide drugs inhibit osteoclasts in vitro and in vivo and also reduces bone resorption in some MM patients. Bortezomib inhibits osteoclasts and activates osteoblast differentiation, reducing bone resorption in MM patients and increasing the receptor activator of nuclear factor kappa-B ligand (RANKL) to osteoprotegerin ratio [68].

Bisphosphonates are the main agent for bone directed therapy in MM. Zoledronic acid, the nitrogen-containing bisphosphonate is likely to have anticancer activity as it improves the PFS and OS of newly diagnosed MM when compared with clodronate [69]. The International Myeloma Working Group recommends that intravenous bisphosphonates be initiated in all patients with active MM and administered in 3–4 weekly intervals to reduce skeletal complications [70].

Denosumab is a fully humanized MoAb that binds to RANKL, inhibiting the interaction with the receptor activator of nuclear factor kappa-B (RANK) receptor and leading to the inhibition of osteoclasts [71]. A phase III study demonstrated the non-inferiority of denosumab to zoledronic acid at delaying time to the first skeletal-related events in MM patients and prolonged PFS [72]. In 2018, the FDA

approved denosumab for use in the prevention of skeletal-related events in MM patients.

1.8 New Agents on the Horizon

Despite the advent of a wide variety of novel agents, MM remains an incurable hematological malignancy with drug resistance an ongoing issue. Research is focused on developing new generations of targeted therapies, finding new targets, and discovering novel targeted therapies with unique mechanisms of action. New drugs currently in phase I and II trials include bispecific T cell or NK cell engager antibodies, CAR T cell therapy, Ulocuplumab (an anti-CXCR4 MoAb), Pembrolizumab (an anti-PD1 MoAb) in combination with radiation therapy, Nivolumab, and various other targeted therapies.

Bispecific antibodies are immunoglobulins that lack fragment crystallizable (Fc) regions and can simultaneously bind to two different epitopes—CD3 molecules on T cells and a specific antigen on myeloma cells—resulting in the destruction of myeloma cells. Currently, there are ongoing early phase clinical trials in RRMM.

Chimeric antigen receptor T cell therapy refers to the adoptive transfer of effector immune cells, either T cells or NK cells, which are engineered to recognize tumor-specific antigens such as the BCMA on myeloma cells and consists of a co-stimulatory molecule [73]. A number of early phase clinical trials of anti-BCMA CAR T cell therapy have reported the safety and toxicity profile in RRMM [74–76].

Ulocuplumab is a CXCR4 chemokine receptor MoAb that induces apoptosis in myeloma cells. In a phase Ib trial, Ulocuplumab, lenalidomide, and dexamethasone showed a high response rate of over 50% in patients with RRMM and who had been previously treated with two lines of therapy including lenalidomide and bortezomib [77].

Several targets have been investigated following the development of pathway receptor inhibitors. These drugs include Vemurafenib (BRAF inhibitor), Dovitinib (FGFR3 inhibitor), Alvocidib and Dinaciclib (targeted kinase inhibitors), Selumetinib (MEK inhibitors), Selinexor (Exportin-inhibitor), and Venetoclax (BCL-2 inhibitor).

Early clinical trials suggest that MM carrying t(11;14) translocations is sensitive to Venetoclax [78]. Currently, Venetoclax, Bortezomib, and dexamethasone are being tested in t [11, 14] RRMM in an ongoing clinical trial.

Selinexor is a selective inhibitor of exportin 1 (XPO1) which blocks export nuclear proteins such as tumor suppressor proteins. It inhibits nuclear factor kappa-B and reduces oncoprotein messenger RNA translation. In an early-phase clinical trial, Selinexor showed a tolerable safety profile and an ORR of 26% [79].

Dinaciclib (cyclin-dependent kinase inhibitor) and Filanesib (kinesin spindle protein inhibitor) have been tested in early phase clinical trials [80–83]. Filanesib was tested in RRMM as monotherapy and in combination with bortezomib and carfilzomib [81–83].

1.9 Conclusion

Although MM remains incurable, the advent of new and novel agents in recent times has transformed it from an acute disease into a chronic condition. However, the increasing availability of therapeutic options is leading to a developing era of drug resistance in MM. To overcome drug resistance and improve patient outcomes, the research and development of improved targeted agents continue. These novel agents and current therapies outlined in this chapter will be further explored in this series.

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