Translational Medicine
ISSN: 2161-1025

Kobayashi et al. Translational Medic 2011, S:2
DOI: 10.4172/2161-1025.S2-002

Review Article Open Access

Clinical Studies of Molecular Targeted Therapy for Multiple Myeloma

Tsutomu Kobayashi, Junya Kuroda*, Miki Kiyota, Ryuko Nakayama and Masafumi Taniwaki

Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, Japan

Abstract

Multiple myeloma (MM) is the second most common hematological malignancy of plasma cells which still remains incurable despite conventional and high-dose chemotherapies. With the introduction of new agents, such as bortezomib, thalidomide, and lenalidomide, there has been significant improvement in treatment outcomes for MM during the last decade. Furthermore, several new novel agents those offer further possibilities for MM patients have become available clinical trials. Nevertheless, it is unclear the appropriate usage of these agents to obtain optimal survivals, for example, whether sequencing of drugs or multi-agent combinations offer the superiority. In this review we will describe the various classes of novel agents being used for MM treatment, including proteasome inhibitors, immunomodulatory drugs, histone deacetylase inhibitors, monoclonal antibodies, and other novel agents, with particularly focus on their mechanisms and clinical efficacy.

Keywords: Multiple myeloma; Proteasome inhibitor; Immunomodulatory drugs; New agents; Clinical study

Introduction

Multiple myeloma (MM) is a malignant plasma-cell disorder that accounts for approximately 10% of all hematologic malignancies. The annual incidence of MM is 2 to 5 per 100,000, and occurs twice as frequently in African-Americans as in Caucasians. The number of deaths from MM had been increasing and the five-year survival rate of MM has remained less than 50%. Despite the development of various combination chemotherapies using cytotoxic agents or high-dose chemotherapy and stem-cell rescue, the overall survival (OS) period did not improve during the last 30 years of the 20th century and MM is still an incurable disease [1]. However, OS of MM has greatly improved during the last decade, mainly due to the introduction of several new agents, such as bortezomib, thalidomide, or lenalidomide. Indeed, patients who were treated with one or more of these novel agents showed significantly longer survival periods from relapse than patients who were not (30.9 vs. 14.8 months; $p<0.001$) [2]. In this article, we review the current knowledge of novel molecular targeted therapies for MM, including proteasome inhibitors, immunomodulatory agents (IMiDs), monoclonal antibodies and other novel agents, with special focus on their mechanisms and clinical efficacy.

Proteasome Inhibitor

Bortezomib

Bortezomib is a modified dipeptidyl boronic acid analogue that binds selectively and reversibly to the β-subunit of 26S proteasome. Inhibition of proteasome blocks protein degradation and leads to excess accumulation of unwanted intracellular molecules. Accordingly, this mechanism is thought to interfere with several signaling pathways which are critical for plasma cell survival and trigger cell suicide programs. The nuclear factor-kappa B (NF-κB) pathway, which positively regulates MM cell survival and proliferation, is considered one of the signaling pathways targeted by bortezomib [3,4], while endoplasmic reticulum stress, which engages the activation of stress-activated protein kinase (SAPK) pathways, has been also shown to be crucial for MM cell death to be brought about by bortezomib [5]. In addition to its direct effect on MM cells, bortezomib has an indirect anti-myeloma effect through acting on the bone marrow tumor microenvironment by inhibiting angiogenesis and the production of cytokines and chemokines which promote MM cell proliferation and survival [3]. In addition, bortezomib has an anabolic effect on bones, thus inhibiting human osteoclast activity and stimulating osteoblast function [6].

The efficacy and safety of bortezomib for MM was initially documented in patients who had relapsed or were refractory to conventional cytotoxic therapies [7-12]. In the phase 3 APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial, bortezomib used as a single agent demonstrated superior efficacy to that of high dose dexamethasone in terms of significantly longer median time to progression (TTP) (6.2 vs. 3.5 months, $p<0.001$), higher response rates (43% vs. 18%, $p<0.001$), and improved survival (1-year survival rates: 80% vs. 67%, $p=0.001$) for relapsed MM patients [7,8]. In the SUMMIT (Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy) trial, a response rate of 28% was achieved and median duration of response (DOR) resulting from the use of bortezomib alone was 12.7 months. The median TTP was 7 months and the median OS 17 months [9,10]. The CREST (Clinical Response and Efficacy Study of bortezomib in the Treatment of relapsing multiple myeloma) study also demonstrated the substantial clinical activity of bortezomib alone or in combination with dexamethasone as the second-line treatment at bortezomib dose levels of both 1.0 and 1.3 mg/m^2 in patients with relapsed or refractory MM [11]. Furthermore, clinical studies with bortezomib-based therapy for newly diagnosed patients indicated promising anti-myeloma effects of this proteasome inhibitor [13-15]. Besides bortezomib alone (or in combination with dexamethasone), several combination therapies with more than three agents including bortezomib have been tried. In a large phase 3 trial, triplet combination therapy using bortezomib, melphalan and prednisolone (MPB, also frequently designated as VMP) demonstrated a significantly superior response rate compared to conventional MP therapy (melphalan and prednisolone), including complete response (CR) of more than 30% (71% vs. 35%, $p<0.001$). Median TTP was also significantly longer for MPB, while the risk of progression was almost halved (24 months vs. 16.6 months, $p<0.001$) [13]. Jagannath et al. [14] also reported bortezomib alone and in combination with

***Corresponding author:** Junya Kuroda MD, PhD, Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto, 602-8566, Japan, Tel. 081 75 251 5740; Fax: 081 75 251 5743 ; E-mail: junkuro@koto.kpu-m.ac.jp

Received October 28, 2011; **Accepted** December 03, 2011; **Published** December 05, 2011

Citation: Kobayashi T, Kuroda J, Kiyota M, Nakayama R, Taniwaki M (2011) Clinical Studies of Molecular Targeted Therapy for Multiple Myeloma. Translational Medic S2:002. doi:10.4172/2161-1025.S2-002

dexamethasone was effective as the frontline treatment for MM. The overall response rate (ORR) in this study was 90%, with 23% of the patients attaining very good partial response (VGPR) and 19% CR/near CR (nCR). After a median follow-up of 49 months, the median OS has not been reached, while the estimated 4-year survival was 67% [14]. The combination therapy using bortezomib, doxorubicin and dexamethasone (PAD) is also an attractive strategy. As the induction therapy before stem cell transplantation for newly diagnosed MM, PAD comprising administration of bortezomib 1.3mg/m^2 (PAD1) or 1.0mg/m^2 (PAD2) on days 1, 4, 8 and 11, of doxorubicin on days 1-4 and dexamethasone 40mg on days 1-4 (plus days 8-11, 15-18, for cycle 1 only) per 21-day cycle induced CR/VGPR in 62% for PAD1 and 42% for PAD2 after induction, and 81% and 53% after transplantation. Progression-free survival (PFS) (29 vs. 24 months), time to re-treatment (36 vs. 29 months) and OS (2-year: 95% vs. 73%) did not differ significantly between PAD1 and PAD2 cohorts, but showed a tendency for PAD1 to be more beneficial than PAD2. Thus, PAD seems to be highly active effective as an induction therapy for newly diagnosed transplant eligible MM patients [15,16]. CyBorD (cyclophosphamide, bortezomib and dexamethasone) is another attractive therapeutic approach. One study reported that response was rapid and the ORR 88%, with VGPR of 61% or better and CR/nCR of 39%. Stem cell harvesting for all patients was successful. Twenty-three patients underwent stem cell transplantation and were evaluable through day 100 with CR/nCR documented in 70% and VGPR in 74%[17]. Furthermore, triplet therapy incorporating both bortezomib and immunomodulatory drugs, such as VTD (bortezomib, thalidomide and dexamethasone) or VRD (bortezomib, lenalidomide and dexamethasone) have shown encouraging clinical results for both treatment-naïve and relapsed MM patients, and we will review their effects in a later section.

One of the most intriguing benefits of bortezomib is its high efficacy against MM harboring cytogenetic abnormalities such as 13q-, t(4;14), t(14;16), or 1q21 abnormality [18]. The only chromosomal abnormality which hampers the clinical effect of bortezomib is 17p-, for which the loss of TP53 is thought to be responsible [19]. However, other pre-treatment factors predictive of clinical response to bortezomib have not been identified yet, while the response to the first and second courses of bortezomib therapy has been suggested to be predictive for longer-term treatment outcome, including late responders [20]. Finally, inclusion of bortezomib into induction therapy prior to high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (HDCT/aPBSCT) yields a better ORR prior to HDCT/aPBSCT, and results in better ORR after HDCT/aPBSCT compared with the use of conventional VAD therapy for induction [21]. Also, the incorporation of bortezomib into the conditioning regimen for HDCT in combination with conventional high-dose melphalan has been shown to be highly effective compared with HDCT using only high-dose melphalan [22].

The most common hematological adverse event associated with bortezomib is thrombocytopenia, accounting for 42% of such events, with Grade 3-4 thrombocytopenia accounting for about 30%. Somewhat different from thrombocytopenia due to genotoxic agents, thrombocytopenia caused by bortezomib is often of short duration and features easy recovery. This may be partly due to bortezomib-induced thrombocytopenia resulting from impaired platelet release from megakaryocytes, but not by a reduction in megakaryocytes [23]. Anemia, neutropenia and lymphocytopenia reportedly account for approximately 21%, 19% and 11%, respectively, of hematologic adverse events following bortezomib (plus dexamethasone) treatment. These events occur more frequently when bortezomib is combined with other cytotoxic agents, such as melphalan, doxorubicin or cyclophosphamide. One of the most intractable non-hematological toxicities is bortezomib-induced peripheral neuropathy (BIPN). Grade 3 BIPN has been observed in up to 13% of patients treated with this agent, with Grade 1-2 in more than half of the patients. In some cases, painful neuropathy may cause significant disability. However, BIPN was found to be reversible in most cases with dose modification or after treatment cessation.

Immunomodulatory Drugs (IMiDs)

Thalidomide

Thalidomide is a glutamic acid derivative with unique properties, such as immunomodulatory effects on cytokine production and T-cell activation, anti-inflammatory and anti-angiogenic functions, inhibition of cell adhesion, and direct inhibition of tumor growth and survival [24]. However, details of the mechanism for the anti-MM effect of thalidomide remain to be fully identified.

A systemic review of the published phase 2 trials of thalidomide monotherapy for relapsed/refractory MM indicated that the ORR was 29.4% (95% CI; 27-32%), and median OS was 14 months. Grade 3-4 adverse events included somnolence (11%), constipation (16%), neuropathy (6%), rash (3%), thromboembolism (3%) and cardiac toxicity (2%) [25]. Alexanian et al. demonstrated that thalidomide plus dexamethasone (TD) resulted in a 47% objective response rates for patients with relapsed/refractory MM, and prolonged OS for patients who showed response [26]. Several other studies also demonstrated the efficacy of TD for relapsed/refractory MM [27,28]. The addition of other chemotherapeutic agents, such as cyclophosphamide or pegylated liposomal doxorubicin, to TD improved the response rates to a ranged of 32-76%, but such combination therapies require a more cautious application because of the higher incidence of adverse events, such as myelotoxicity or thrombotic events [29-31].

Two phase 3 trials, ECOG E1A00 and MM003, for newly diagnosed MM patients demonstrated that the response rates to TD were significantly higher than those to high-dose dexamethasone (HDD) (63% vs. 41%, p=0.002 in the ECOG E1A00 trial and 63% vs. 46%, p<0.0005 in the MM003 trial) in addition to higher CR and VGPR rates for TD. In addition, PFS of the TD cohort was significantly longer in the MM003 trial (14.9 vs. 6.5 months, p<0.001) [32,33]. Cavo et al. [34] also demonstrated that TD is superior to VAD in terms of ORR (76% vs. 52%, p<0.001), while granulocytopenia occurred more frequently with VAD (12%), but nonfatal deep vein thrombosis more frequently with TD (15%). Peripheral blood stem cell collection was nearly equally successful following either TD or VAD [34]. In the prospective phase 3 HOVON-50/GMMG-HD3 trial, TAD (thalidomide, doxorubicin, dexamethasone) was shown to produce significantly higher ORR compared with VAD (72% vs. 54%, p<0.001) and higher CR and VGPR rates before HDCT/aPBSCT. Although ORRs after HDCT/aPBSCT were not significantly different for the two arms, the CR plus VGPR rate was significantly higher for the TAD cohort (49% vs. 32%, p<0.001) [35]. Four large trials have shown the superior effect of thalidomide in combination with conventional melphalan and prednisolone (MPT) to MP alone in elderly transplant-ineligible patients [36-39]. In the GIMEMA study, Palumbo et al. demonstrated that the median PFS was 21.8 months for MPT and 14.5 months for MP (p=0.004), while the median OS was not significantly different [36]. In the IFM99-06 trial, the median OS was 33.2 months for MP, 51.6 months for MPT, and 38.3 months for MEL100 (melphalan 100mg/m^2). The PFS of the MPT cohort was significantly longer than that of the

MP cohort (p=0.0006) and MEL100 cohort (p=0.027), while there was no significant difference in OS between the MP and MEL100 cohorts (p=0.32) [37]. In the IFM01-01 study, OS was significantly longer for patients treated with MPT than for those treated with MP (median, 44.0 months vs. 29.1 months, p=0.028), as was PFS (median, 24.1 months vs. 18.5 months, p=0.001) [38]. The HOVON49 study also established improvement of ORR by treatment with MPT compared with MP (ORR; 66% vs. 45%, p<0.001, VGPR; 27% vs. 10%, p<0.001) [39]. Most clinical trials have thus produced better ORR for MPT than for MP, although the former's long-term effects are still controversial. While some studies have demonstrated longer PFS and OS for MPT than for MP, other studies did not find any significant improvement in long-term efficacy for MPT [40,41]. It has been postulated that the survival period following the re-progression of MM after MPT is significantly shorter than that after MP. TD was also shown to produce higher ORR compared with MP (68% vs. 50%, p=0.002). However, again, there were no significant differences in TTP and PFS between TD and MP, while OS was significantly shorter for the TD group (41.5 vs. 49.4 months, p=0.024). Toxicity was higher with TD, particularly in patients over 75 years old with poor performance status [42]. It should be noted that high-dose dexamethasone and an increased dose of thalidomide were associated with more severe toxicity in elderly patients. These findings collectively, therefore, show that thalidomide as front-line therapy is still not fully supported.

On the other hand, the efficacy of thalidomide as maintenance (or consolidation) therapy has been widely recognized, in particular as maintenance therapy after HDCT. In the IFM99-02 randomized trial, 3-year post-randomization probability of event-free survival (EFS) (52% vs. 36%) and 4-year post-diagnosis probability of survival (87% vs. 77%) were significantly higher for patients who received thalidomide maintenance after high-dose therapy [43]. The survival benefits of thalidomide maintenance have been also reported in several other clinical studies, such as the SWOG S0204 trial and Total Therapy 2 [44-47]. Importantly, the benefit of post-HDCT thalidomide therapy was observed only in patients who failed to attain VGPR after HDCT/aPBSCT. It should also be noted that the survival after relapse of patients with a history of thalidomide treatment was significantly shorter [45]. These findings indicate the need for more evidence before the optimal indication, dosage and duration of thalidomide therapy following HDCT/aPBSCT in MM can be decided.

Lenalidomide

Lenalidomide, a derivative of thalidomide, is a second-generation IMiD that is chemically similar to thalidomide but is more potent and has fewer adverse effects. Compared with thalidomide, lenalidomide inhibits the growth factors for MM cells approximately 50,000 times more effectively, while it activates anti-MM immune reaction approximately 200-1,000 times more effectively [48]. On the other hand, the anti-angiogenic effect of lenalidomide is considered to be less than that of thalidomide. Phase 1 and 2 trials of lenalidomide as a single agent for treatment-refractory MM showed that ORRs were 24% and 29%, respectively, and that median OS was approximately 27 months. Significant peripheral neuropathy and deep vein thrombosis each occurred in only 3% of patients, which was markedly less than those caused by thalidomide, while an important finding was that even thalidomide- or bortezomib-resistant patients responded to lenalidomide [49,50]. Two phase 3 randomized multicenter trials, MM-009 and MM-010, demonstrated the superior effect of lenalidomide plus dexamethasone (RD) compared to that of placebo plus dexamethasone on previously treated MM patients [51,52]. In both trials, ORR was significantly higher for the lenalidomide than the placebo group (61.0% vs. 19.9%, p<0.001 for MM-009 and 60.2% vs. 24.0%, p<0.001 for MM-010). The median TTP (11.1 vs. 4.7 months, p<0.001 for MM-009 and 11.3 vs. 4.7 months, p<0.001 for MM-010) and OS (29.6 vs. 20.2 months, p<0.001 for MM-009, while "not reached" vs. 20.6 months, p=0.03 for MM-010) were also significantly longer for the lenalidomoide group. RD was similarly effective, regardless of prior treatments with HDCT/aPBSCT or with bortezomib-based treatment, and was also successful for patients who had previously failed thalidomide.

RD was shown to be also effective for newly diagnosed MM patients, with an overall objective response rate (better than stable disease [SD]) of 91% [53]. Niesvizky et al. [54] demonstrated that the addition of clarithromycin (Biaxin) to RD (BiRD) was an effective regimen for newly diagnosed MM. The ORR for this regimen was 90.3% with a combined stringent CR and CR rate of 38.9%, while the better than VGPR rate was 73.6% [54]. An important finding reported by the MM-016 trial was that lenalidomide may overcome poor prognostic features of MM resulting from adverse cytogenetic abnormalities such as deletion of 13q and t(4;14). On the other hand, patients with deletion of 17p13 showed significantly worse outcomes [55]. In a phase 3 open-label randomized controlled trial by ECOG, low-dose dexamethasone (40mg once weekly) in combination with lenalidomide (25mg on days 1-21, 28-day cycle) was compared with high-dose dexamethasone (40mg on days 1-4, 9-12, 17-20) plus lenalidomide for patients with untreated MM. Although the CR or PR rates within four cycles for the low-dose dexamethasone group were lower than those for the high-dose dexamethasone group (68% vs. 79%, p=0.008), the 1-year OS was significantly higher for the low-dose dexamethasone group (96% vs. 87%, p=0.0002) and toxicity was significantly lower [56]. The combination of MP and lenalidomide (MPR) followed by lenalidomide maintenance proved to be a promising first-line treatment for elderly MM patients. With this regimen, 81% of patients attained at least PR (47.6% for VGPR and 23.8% for CR), while 1-year EFS and OS were 92% and 100%, respectively. When combined with MP, the dose of lenalidomide should be decreased to 10mg/day (40% when used in the conventional RD setting), because of myelotoxicity. With this dose modification, the toxicity of MPR was adequately manageable and aspirin seemed to be effective as anti-thrombosis prophylaxis. Although ORR resulting from MPR is much superior to that from MP, PFS did not improve in response to MPR only. It should be noted that the addition of lenalidomide maintenance has the advantages of producing a higher ORR by MPR and a longer PFS than with MP only [57]. Lenalidomide in combination with other cytotoxic agents has also proven to have a favorable effect on relapsed/refractory MM patients resulting in high response rates of approximately 70%. However, the adverse events associated with these combination therapies, especially hematological toxicities such as neutropenia and thrombocytopenia, are considerable [58-60].

Two randomized trials by the Cancer and Leukemia Group B (CALGB) and Investigators in a large French intergroup (IFM) also demonstrated the high efficacy of lenalidomide as maintenance treatment [61,62]. However, analysis of adverse events disclosed a higher incidence of secondary primary cancers (SPCs) for patients who were treated with lenalidomide rather than placebo. Thus, the indication of maintenance therapy with lenalidomide should be carefully determined for individual patients, in accordance with their disease status and background, such as age.

Combination therapies of proteasome inhibitor and IMiD

The aforementioned novel agents exert their anti-myeloma activities *via* different mechanisms and thus their combinations may

be expected to further enhance each other's anti-myeloma properties. Indeed, the synergistic anti-myeloma activities of the novel agents such as bortezomib and lenalidomide have been demonstrated in several preclinical studies. At the same time, there is concern about increased toxicity as result of combining these new agents. We here review the current knowledge of some of the most promising combination therapies using novel anti-myeloma agents.

First, the combinations of bortezomib with thalidomide have proven to be effective for both relapsed and newly diagnosed MM patients. The combination of bortezomib, thalidomide and MP (VMPT) has shown an encouraging effect on relapsed MM with manageable toxicity [63]. Also, VMPT followed by maintenance with bortezomib-thalidomide (VT) was found to be superior to VMP alone for patients with untreated MM who were ineligible for HDCT/aPBSCT [64]. The combination of bortezomib, melphalan, dexamethasone and intermittent doses of thalidomide (VMDT) has also demonstrated a favorable effect on relapsed/refractory MM. The ORR by VMDT was 66%, including 13% CR, 27% VGPR and 26% PR, and the median TTP was 9.3 months. Common adverse events included cytopenia, peripheral neuropathy and infection, but no patient experienced deep-vein thrombosis [65]. The effect of bortezomib plus TD (VTD) was compared with TD alone as induction therapy before and as consolidation therapy after tandem HDCT/aPBSCT in newly diagnosed MM in a randomized phase 3 study. VTD induction therapy significantly improved the rate of CR plus nCR (31% with VTD vs. 11% with TD, $p<0.0001$) before aPBSCT, although Grade 3-4 adverse events occurred more frequently with VTD than with TD (56% vs. 33%, $p<0.0001$) [66]. VTD has also been incorporated in Total Therapy 3 (TT3), and this study demonstrated that VTD could be safely combined with multi-agent chemotherapy. In the case of TT3, the induction strategy prior to tandem HDCT/aPBSCT consisted of VTD-PACE (bortezomib, thalidomide, dexamethasone and 4-day continuous infusion of cisplatin, doxorubicin, cyclophosphamide, etoposide) and 3-year maintenance therapy with VTD for the first year and TD for the remaining two years. At 24 months, 83% of patients achieved nCR, and 88% maintained their CR response for 2 years from disease onset. With a median follow-up of 20 months, 2-year estimates of EFS and OS were 84% and 86%, respectively. Toxicities worse than Grade 2 included thrombo-embolic events in 27% and peripheral neuropathy in 12% of the patients [67]. The combination of lenalidomide and bortezomib showed significant activity for relapsed/refractory MM including patients who were previously treated with bortezomib or IMiDs. In one phase 1 study, the combination of bortezomib, lenalidomide and dexamethasone (VRD) produced minimal response (MR) or better in 61% of relapsed/refractory MM [68]. Another study which compared the effects of VRD and RD showed that ORR for VRD was 63% which was similar with that for RD. Also, both the median PFS and OS were similar for RD and VRD. Poor risk cytogenetics were associated with lower response rates for RD, but not for VRD. However, prognosis for patients with deletion of 17p remained extremely poor even when they were treated with VRD combination [69]. Interesting results for a combination regimen of two IMiDs, thalidomide and lenalidomide, was recently reported by Palumbo et al. This multi-center, open-label, non-comparative phase 2 trial evaluated the safety and efficacy of salvage therapy with lenalidomide, melphalan, prednisone and thalidomide (RMPT) followed by lenalidomide maintenance for patients with relapsed/refractory MM. Of the 44 patients, 75% achieved at least PR, including 32% VGPR and 2% CR. The 1-year PFS and OS were 51% and 72%, respectively. Major adverse events were neutropenia (18%), infection (14%), thrombocytopenia (7%), and fatigue (7%). No Grade 3-4 thromboembolic events or peripheral neuropathy was reported [70].

Potential new Agents undergoing Clinical Trials

Proteasome inhibitor

Carfilzomib: Carfilzomib is an irreversible proteasome inhibitor from a new chemical class called peptide keto epoxides which require an N-terminal threonine to bind, so the binding of carfilzomib is highly restricted to proteasomes. This high binding selectivity prevents it from exerting off-target activity on other non-proteasome cellular proteases. Through this mechanism, carfilzomib selectively inhibits proteasome functions and potently induces apoptosis in cancerous cells, including MM cells [71].

Two phase 2 clinical trials of carfilzomib have been reported [72,73]. In one clinical trial for 46 relapsed/refractory MMs, 20 mg/m^2 carfilzomib induced response in 26% (10/39) of evaluable patients, including 5 PR and 5 MR, and SD in 16 patients. Most responses were observed within the first cycle [72]. In the other study, ORR with carfilzomib was 54% for 14 evaluable bortezomib-naïve patients, including 1 CR and 2 VGPRs, while ORR of bortezomib-exposed patients was much inferior to that of bortezomib-naïve patients. The most common non-hematologic adverse events were fatigue (61%), nausea (58%), vomiting (36%), and insomnia (32%). Grade 3-4 hematological adverse events occurred in 10% or less of patients. Importantly, peripheral neuropathy was much less frequently accompanied with carfilzomib compared with bortezomib [73].

IMiDs

Pomalidomide

Pomalidomide, a derivative of thalidomide, is the newest IMiD agent, which also possesses anti-myeloma activity [74]. Compared with thalidomide, the activity of pomalidomide against tumor necrosis factor (TNF)-α is some 1,000-10,000 times stronger, its effect on T-cell activation and proliferation about 50-2,000 times stronger, and its production of interleukin (IL)-2 and interferon-γ about 50-100 times greater. It has been reported that pomalidomide (2mg daily) plus low-dose dexamethasone (40mg weekly) (Pom/Dex) was highly effective against relapsed MM, even in the case of lenalidomide refractory patients, with an ORR of 47%. In this study, the median DOR and the median OS were 9.1 months and 13.9 months, respectively [75]. Furthermore, it was demonstrated that Pom/Dex was also effective for patients who were refractory to both bortezomib and lenalidomide (so called "dual refractory myeloma"). In this phase 2 trial, the efficacy of two doses of pomalidomide, 2mg/day and 4mg/day, was compared with that of dexamethasone 40mg weekly. The ORR was 49% for the 2mg cohort and 43% for the 4mg cohort, while the corresponding median PFS was 6.5 months (95%CI: 3.9-8.9) and 3.2 months (95%CI: 1.9-8.6), and the OS at 6 months 78% (95%CI: 65-94) and 67% (95%CI: 52-86). These data thus showed no advantage for 4mg/day over 2mg/day. The most common toxicity with Pom/Dex was myelosuppression, including Grade 3-4 neutropenia for 51-66%. The most common non-hematological adverse event was fatigue with Grade 3-4 fatigue for 9%. Deep vein thrombosis was infrequent for the majority of the patients who received aspirin for thromboprophylaxis [76].

Histone Deacetylase (HDAC) Inhibitors

Vorinostat

Vorinostat (suberoylanilide hydroxamic acid, SAHA) is a member of histone deacetylase (HDAC) inhibitors which possess a broad spectrum of epigenetic activities. Vorinostat has been already approved by the Food and Drug Administration (FDA) for the treatment of

cutaneous T-cell lymphoma. A phase 1 trial of oral vorinostat for relapsed/refractory MM was conducted to determine maximum tolerated dose (MTD) and assess its anti-myeloma activity and safety, but the study could not be completed due to early termination by the sponsor. In this study, the major adverse events included fatigue, anorexia, dehydration, diarrhea and nausea [77]. In another phase 1 trial, vorinostat in combination with bortezomib for relapsed/refractory MM was investigated. ORR was 42%, including three PRs by nine bortezomib refractory patients. The most common Grade 3-4 toxicities were myelosuppression, fatigue, and diarrhea [78]. The efficacy of vorinostat in combination with bortezomib is currently under investigation in other clinical trials.

Panobinostat

Panobinostat is a potent pan-deacetylase inhibitor that targets HDAC6, disrupts aggresome and heat shock protein 90 (HSP90) activity, and promotes MM cell death. The combination of panobinostat and bortezomib has been shown to produce synergistic cytotoxicity in preclinical studies of its use for MM [79]. A phase 1b study of the combination of panobinostat with bortezomib for MM displayed a feasible toxicity profile and an ORR of 36%, including 8 (57% of all responders) bortezomib-refractory patients [80]. This combination is to be further evaluated in the PANORAMA program (PANobinostat ORAl in Multiple myelomA) consisting of PANORAMA 1 and PANORAMA 2. PANORAMA 1 is a prospective, multinational, randomized, double-blind, placebo-controlled phase 3 study to compare the efficacies of a panobinostat plus bortezomib/dexamethasone regimen and a placebo plus bortezomib/dexamethasone regimen for previously treated MM. PANORAMA 2 is a U.S.-based, multicenter, single-arm phase 2 study to evaluate the efficacy of the combination of panobinostat and bortezomib/dexamethasone for relapsed MM and bortezomib-refractory MM to assess if the addition of panobinostat can re-sensitize bortezomib-refractory MM to bortezomib [81].

Monoclonal Antibodies

Elotuzumab and dacetuzumab

Potential targets of monoclonal antibody therapy include growth factors and their receptors, other signaling molecules, and antigens expressed exclusively or predominantly on MM cells. Monoclonal antibody therapy has demonstrated its anti-tumor activity *via* a range of mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity, interference with receptor-ligand interactions, and monoclonal antibody conjugation to radioisotopes or toxins. A number of potential antigen targets are being investigated in the context of MM treatment, and several of those are currently the subject of investigation in clinical trials [82]. We focus here on the most promising two monoclonal antibody therapies for MM, elotuzumab and dacetuzumab.

Elotuzumab (HuLuc63) is a humanized monoclonal antibody targeting CS-1, which is a cell surface glycoprotein universally (>95%) expressed at high levels on MM cells but at limited levels on normal tissues [83]. Elotuzumab has demonstrated significant anti-tumor activity in pre-clinical mouse models of MM, and its anti-myeloma effect was shown to be enhanced by bortezomib or lenalidomide [84, 85]. In a phase 1 study of monotherapy, the anti-myeloma activity of elotuzumab was modest, as elotuzumab induced SD in 6 of 23 patients [86]. However, a surprisingly favorable effect of the combination of elotuzumab and RD was observed in another phase 1 study, since this combination induced ORR in 82% of relapsed/refractory MM patients (96% of lenalidomide-naïve patients), while the median time to progression was not reached. The most frequent Grade 3-4 toxicities were neutropenia (36%) and thrombocytopenia (21%) [87]. A larger phase 2 study is ongoing to determine the rate and durability of the responses observed in this phase 1 trial.

Dacetuzumab is a humanized anti-CD40 monoclonal antibody with multiple action mechanisms. CD40 is a member of the TNF receptor superfamily which is highly expressed on MM cells. Dacetuzumab exhibits its anti-tumor activity *via* ADCC and induction of apoptosis. In a phase 1 study, dacetuzumab monotherapy induced SD as the best clinical response in only 9 of 44 patients (20%). Adverse events included symptoms associated with cytokine release syndrome and elevated hepatic enzymes [88]. Two other trials for a combination therapy including dacetuzumab are ongoing.

Other Categories

Bendamustine

The alkylating agent bendamustine is structurally similar to both alkylating agents and purine analogs and shows no cross-resistance with other agents, including alkylators. The efficacy of bendamustine has been observed not only for non-Hodgkin lymphoma and chronic lymphocytic leukemia, but also for MM. Knop et al. [89] demonstrated the efficacy and toxicity of bendamustine (100mg/day in day1, 2) for MM patients who had relapsed after HDCT. In this study, ORR was 55% with the median PFS for 26 weeks. The major adverse event associated with bendamustine was myelosuppression [89]. In a phase 3 randomized study comparing the efficacy of bendamustine plus prednisolone (BP) and standard MP for newly diagnosed MM, BP was found to be superior to MP with respect to CR rate, time to treatment failure, cycles needed to achieve maximum remission and quality of life [90]. These results suggest that BP is a candidate for use in the treatment of treatment-naïve MM patients who are not eligible for HDCT/aPBSCT.

Perifosine

Perifosine is an oral, novel synthetic alkylphospholipid, which targets multiple signal transduction molecules. It potently inhibits Akt, while it activates JNK. *In vitro* studies showed that perifosine induces cytotoxicity in both MM cell lines and patient-derived MM cells resistant to conventional therapies, while it augments the anti-myeloma effects of dexamethasone and bortezomib [91]. In a phase 2 trial, perifosine as a monotherapy showed modest activity, but its effect on relapsed/refractory MM became significant when it was combined with dexamethasone. This combination resulted in PR plus MR of 38% and SD of 47% of evaluable patients. This combination therapy was generally well tolerated, although caution was warranted for patients with renal dysfunction. Other studies of perifosine in combination with bortezomib and with lenalidomide are currently underway [92].

Tanespimycin

Tanespimycin (KOS-953, 17-AAG) is an inhibitor of HSP90, which is a molecular chaperone of client proteins, such as IL-6, or insulin-like growth factor 1 receptor (IGF-1R), which are essential for growth, survival and drug resistance of MM cells. In a phase 1b trial for relapsed/refractory MM, tanespimycin combined with bortezomib induced CR, PR and MR response in 71% of bortezomib-naïve MM patients, in 33% of bortezomib-refractory MM patients, and in 38% of bortezomib pretreated MM patients [93].

Summary

Novel agents, such as bortezomib, thalidomide and lenalidomide,

have altered the landscape of therapeutic strategies for MM and have improved the survival of MM patients. Furthermore, these novel agents may overcome poor prognostic cytogenetic abnormalities such as 13q deletion or t (4;14), and the multi-drug combination therapies including these novel agents generally produce higher response rates and would be favorable for patients who require rapid disease control. Combinations with new drugs can be expected to become the backbone of MM treatment in the near future. Nevertheless, it remains unclear whether multi-agent combination therapy as the front-line therapy actually results in longer OS. It is not clear either which sequence of novel agents is the best to obtain optimal OS. In conclusion, currently available new drugs have shown encouraging effects on MM in clinical trials, while a number of other molecular targeting agents are currently undergoing testing for clinical use. It is expected that the menu of therapeutic strategies for MM will further expand and that patient outcomes will continue to improve a result of further development of new other molecular targeting drugs and determination of the optimal use of these agents.

Acknowledgment

This work was partly supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and by grants from the Kobayashi Foundation of Innovative Cancer Chemotherapy, and the Award in Aki's Memory from the International Myeloma Foundation (MT and JK).

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