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Progress in Drug Therapy for Multiple Myeloma

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ABSTRACT Multiple myeloma remains incurable with conventional treatments. However, new active drugs, including the immunomodulatory agents, thalidomide and lenalidomide, and the proteasome inhibitors bortezomib and NPI-0052, and other targeted therapies, have shown promising anti-myeloma activity. These agents represent a new generation of treatments for multiple myeloma that affect both specific intracellular signaling pathways and the tumor microenvironment. This review therefore focuses on the extensive clinical data available from studies of these drugs in the treatment of newly diagnosed, refractory and relapsed multiple myeloma.

KEY WORDS: multiple myeloma, therapy, immunomodulatory, proteasome inhibitor, targeted therapies.

Introduction

Multiple myeloma (MM) is a B-cell malignancy with a terminally differentiated plasma cell phenotype. The characteristic findings in MM are lytic bone disease, renal insufficiency, anemia, hypercalcemia, and immunodeficiency. The most common presenting symptoms are fatigue, bone pain, and recurrent infections. The disease is considered incurable and conventional therapy results in complete remission in only 5% of patients with overall median survival only about 36 months. The number of therapeutic options in the treatment of MM has increased dramatically since the beginning of the millennium, and prospects for the future are even more encouraging.

From the 1960s until very recently, conventional therapy for patients with MM was glucocorticoid based in combination with alkylating agents and/or anthracyclines. Melphalan plus prednisone (MP) has been the gold standard for treatment over the last 40 years. Cumulative exposure to melphalan, however, is associated with an increased risk of marrow toxicity, including myelodysplasia, acute leukemia, and impaired stem cell production. This is an important consideration in patients who are candidates for high-dose therapy with stem cell rescue (autologous transplants). Variations of the MP regimen (eg. vincristine, BCNU, melphalan, cyclophosphamide and prednisone) have not proven to be superior. With conventional therapy, approximately 5% of the patients achieve complete remission (CR). Salvage therapy for relapsed or primary refractory disease initially utilized the vincristine plus doxorubicin plus dexamethasone (VAD) regimen. This produced response rates of 40% to 50% in relapsed disease, and about 30% in patients with primary refractory disease. The most active agent in the combination is dexamethasone. High-dose dexamethasone pulsing alone induces responses in about 30% to 50% of patients, regardless of the prior response. New agents include the proteasome inhibitor bortezomib (Velcade) and NPI-0052, the antiangiogenic and immunomodulator thalidomide (Thalomid) and

its analog lenalidomide (Revlimid), and other targeted therapies. Clinical studies have shown encouraging results first in patients with relapsed/refractory MM, then in newly diagnosed patients. These drugs, alone and in combination, are now all approved treatment options for symptomatic MM.

Immunomodulatory agents

Thalidomide

Thalidomide has been banned from widespread clinical use since 1962 because of severe teratogenicity. It was introduced in the treatment of advanced MM in the late 1990s, because of its antiangiogenic properties. Thalidomide blocks the ability of vascular endothelial growth factor (VEGF) and fibroblast growth factor-β (β-FGF) to stimulate neovascularization of bone marrow. Thalidomide directly inhibits the growth and survival of myeloma cells, modulates some adhesion molecules, inhibits tumour necrosis factor-α (TNF-α) and interleukin 6 (IL-6) secretion. Thalidomide appeared to be highly effective in refractory and relapsed myeloma. In a phase II study and its update on 169 patients (most of whom had failed high-dose therapy), a 30% partial response (PR) and a 14% near complete response (nCR) were observed. A 2-year follow-up showed 20% and 48% event-free survival (EFS) and OS rates respectively. Many other studies have demonstrated the efficacy of thalidomide as a single agent in advanced MM with the response rate ranging from 25% to 64%[1].

Thalidomide plus dexamethasone: MM patients were treated with low-dose THAL (100 mg/day) continuously and DEX 40 mg, days 1~4, every month[2]. From June 1999 to August 2000, 77 patients (median age 65 years) who had relapsed or were refractory to chemotherapy were treated. Fourteen patients (18%) showed a myeloma protein reduction of 75%~100%, 18 patients (23%) showed a reduction of 50%~75%, 19 patients (25%) a response of 25%~50% and 26 patients (34%) a response of < 25% or disease progression. After a median follow-up of 8 months, median progression-free survival was 12 months. THAL was well tolerated.

Thal-Dex-pegylated liposomal doxorubicin (Doxil): The addition of Doxil to Thal-Dex increased the rate of objective responses up to over 70%[3]. In a recent prospective multicenter phase II study, 50 patients received Thal-Dex and Doxil (40 mg/m^2). The overall response (OR) rate was 92%, with 26% CR, 6% nCR and 44% PR. The median progress-free survival (PFS) and EFS were 22 months and 17 months, respectively.

A regimen that included cyclophosphamide (Cy) with Thal-Dex showed objective responses in 79% of the 52 patients (17% of them reaching a CR). This combination can induce a stable plateau phase and prolong stable disease.

In a comparative case-control study of 200 patients, the superiority of Thal-Dex over VAD was reported with a significantly higher response rate (76% *vs.* 52%; $P < 0.001$)[4]. Recently, in a phase III randomised study, a Thal-Dex combination therapy was compared to Dex alone in 207 patients eligible for ASCT. The OR was significantly higher with Thal-Dex than Dex alone (63% *vs.* 41% respectively, $P = 0.0017$), with CR in 4% of the patients. Disease progression was noted in 2% of the patients with Thal-Dex and 5% of the patients with Dex alone[5].

In addition to known teratogenicity, the frequent adverse events are as follows: sedation, somnolence, constipation, nausea, fatigue, cutaneous rash, bradycardia, hypothyroidism and edema. The most serious complications are peripheral neuropathy and venous thromboembolism.

Lenalidomide

Lenalidomide is an analogue of thalidomide that has been shown to be more potent than thalidomide in the stimulation of T-cells, interleukin-2, and interferon-gamma production. Both drugs have direct cytotoxic effects on myeloma cells and are capable of inducing apoptosis. They are also capable of reducing angiogenesis through the inhibition of the secretion of vascular endothelial growth factor (VEGF). Inhibition of VEGF leads to alterations in the microvasculature of the bone marrow environment, and inhibits myeloma cell growth and proliferation. It also down-regulates the activity of NF-κB.

Results from phase I and II studies have shown lenalidomide to have significant and durable single-agent activity in relapsed and refractory multiple myeloma[6-11], with responses seen in 14%~29% of the patients. Two randomized phase III trials have demonstrated that a lenalidomide plus dexamethasone regimen provides greater efficacy than with dexamethasone alone[6,7]. In the North American phase III trial[6], the response rate was greater with lenalidomide plus dexamethasone than with dexamethasone alone (59% *vs.* 21%), as was the CR rate (13% *vs.* < 1%). The median TTP (11.1 months *vs.* 4.7 months) and median OS time (29.6 months *vs.* 20.2 months) were also longer with lenalidomide plus dexamethasone than with dexamethasone alone. These findings were corroborated by results from an identical European phase III trial[7]. In that study, the observed response rate was again 59%, with lenalidomide plus dexamethasone, compared with 24% for dexamethasone alone, and the CR/nCR rates were 17% and 4%, respectively. Again, the median TTP and OS time were longer with lenalidomide plus dexamethasone than with dexamethasone alone.

The results of a phase II trial have shown that lenalidomide plus dexamethasone has promising activity in a frontline setting. The response rate in 31 evaluable patients was 91%, including a 38% CR/nCR rate[10]. Based on these findings, two cooperative groups are currently

assessing lenalidomide plus dexamethasone as frontline therapy for multiple myeloma patients in randomized phase III trials. Mirroring the therapeutic approach taken with bortezomib and thalidomide, lenalidomide is also being assessed in combination with MP in elderly patients with newly diagnosed multiple myeloma. Preliminary results show that the combination produces a response rate of 85% after a median of treatment cycles, including a 17% CR/nCR rate[11].

Other lenalidomide-based regimens under investigation in the relapsed setting include lenalidomide plus doxorubicin and dexamethasone[8], and lenalidomide plus liposomal doxorubicin, vincristine, and dexamethasone, with the latter producing a response rate of 75%, including a 29% CR/nCR rate (SWOG criteria)[9].

Unlike thalidomide, lenalidomide has almost no sedative or constipative properties, and induces only minimal neurotoxicity. The most common adverse event is myelosuppression, particularly neutropenia and thrombocytopenia ≥ 3 grade. But lenalidomide is also associated with a high risk of deep vein thrombsis (DVT) when it is used with other agents, especially high-dose Dex. However, administration of aspirin or salicylates seems to reduce the risk of DVT.

Proteasome inhibitors

Bortezomib

The proteasome regulates protein turnover in eukaryotic cells. The ubiquitin-mediated proteasome degradative pathway regulates a large repertoire of intracellular proteins that finally control the cell cycle, tumor growth and survival. Bortezomib is representative of a class of peptide boronate proteasome inhibitors, which targets the 26S proteasome, a multicatalytic proteinase complex involved in intracellular protein degradation. Bortezomib has high affinity, specificity and selectivity for proteasome catalytic activity. It ultimately inhibits the activation of the transcription factor NF-κB by protecting its inhibitor (IκB) from degradation by the proteasome complex.

NF-κB has been reported to play a growth and anti-apoptotic role in multiple myeloma. Myeloma cell adhesion to stromal cells induces a NF-κB dependent up-regulated transcription of IL-6, a growth and anti-apoptotic factor. NF-κB is inhibited by the association with IκB inhibitors: the phosphorylation of the IκB inhibitor induces their degradation by the 26S proteasome. Bortezomib can directly induce apoptosis of primary and drug-resistant myeloma cell lines by interfering with the caspase-dependent pathway, by down-regulating IL-6 and up-regulating p53 and the cell-cycle inhibitor p27.

In phase II trials, SUMMIT and CREST, it was found that treatment with bortezomib, alone or in combination with dexamethasone, produced durable responses with meaningful survival benefits in patients with relapse and/or refractory multiple myeloma. The international, randomized phase III Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial in patients with relapsed multiple myeloma following 1~3 prior therapies, showed that single-agent bortezomib provides a significantly longer time to progression , higher response rate, and superior survival compared with high-dose dexamethasone[12]. More recently, in an updated analysis of the APEX trial after extended follow-up (median, 22 months), the median overall survival (OS) time was 29.8 months with bortezomib *vs.* 23.7 months with dexamethasone. Overall response (43%) and complete response [complete response/near complete response (CR/nCR), 15%] rates with bortezomib were also higher in the updated analysis than at initial analysis.

Substantial activity has also been demonstrated in studies of bortezomib in combination with other commonly used agents for multiple myeloma. In a phase I/II trial on 35 patients, which included the association of bortezomib plus low doses of oral melphalan, CR and PR were achieved in 47% (6% of CR and 9% of nCR)[13]. Median PFS was 8 months. The addition of Dex to this combined therapy improved response rates up to 80%. In a phase I study on 22 evaluable patients, the association of bortezomib and Doxil demonstrated significant antitumour activity in advanced MM, with an OR rate of 73%, including 36% of CR or nCR[14]. Actually, a multicenter randomized phase III study on 646 patients comparing the combination of Doxil and bortezomib vs. bortezomib alone has confirmed this encouraging result[15].

In a recent multicenter phase I/II study, Palumbo et al.[16] evaluated the efficacy and tolerability of VMPT(Bortezomib-MP-Thal) on 30 patients to identify the most appropriate and effective dose of bortezomib in the MPT regimen. The maximum tolerated dose of bortezomib was 1.3 mg/m^2. Sixty-seven percent of the patients achieved a PR and 43% of these had a very good partial response (VGPR). A CR was observed in the subset of patients who received this regimen as second-line treatment (36%). The 1-year PFS and 1-year OS were 61% and 84%, respectively.

Bortezomib is currently being evaluated as a first-line treatment in previously untreated patients either ineligible or candidates for ASCT in ongoing clinical trials. In the front-line setting, bortezomib was studied as a single agent in a multicenter phase II study in 63 patients (46 of them evaluable for response) with a median age of 60 years[17]. Results showed 11, 20 and 28% of patients obtained a complete, partial and minimal response respectively, giving an OR rate of 59%.

The toxicity profile of bortezomib is mainly characterised by peripheral neuropathy and thrombocytopenia. Clinical manifestations include paraesthesias, numbness and pain affecting especially the lower extremities. Overall, the investigators reported that 37% of the patients had developed a dose-related peripheral neuropa-

thy of some grade with 14% of grade ≥ 3 within the 5 five cycles of treatment.

NPI-0052

NPI-0052 is a novel proteasome inhibitor. Like bortezomib, NPI-0052 triggers apoptosis in MM cells, but is distinct from bortezomib in its chemical structure, effects on proteasome activities, and mechanism of action. In vitro, both NPI-0052 and bortezomib-triggered apoptosis is associated with sequential occurrence of proteasome inhibition, but with different kinetics. The cellular response to NPI-0052 occurs much earlier than that of bortezomib. A recent preclinical study demonstrated that orally administered NPI-0052 is cytotoxic to MM cells, with reduced toxicity against normal cells compared with bortezomib[18]. It is currently being evaluated in a phase I trial. Ultimately, these 2 proteasome inhibitors may be combined since they have different kinetics and cellular responses.

Monoclonal antibodies

Anti-IL-6, tocilizumab

IL-6 is involved in multiple pathways in myeloma; secretion occurs from malignant plasma cells, as well as from the microenvironment, resulting in autocrine and paracrine stimulation. This results in myeloma cellular proliferation. Tocilizumab, a humanized anti-IL-6 receptor Mab that specifically blocks IL-6 cell-to-cell signaling, is currently being studied in MM. A recent study by Yoshio-Hoshino et al.[19] demonstrated in a murine MM model the effectiveness of tocliuzumab in vitro and in vivo.

Other targeted therapies

Arsenic trioxide

Arsenic trioxide (ATO) has been used as a medical treatment in Asia for thousands of years, and it is now approved for the treatment of relapsed acute promyelocytic leukemia based on positive results from a multicenter US trial[20].

ATO inhibits MM cell proliferation possibly through the induction of a p21 cyclin dependent kinase inhibitor protein. It also induces apoptosis in MM cells through an increase in caspase-3 activity. The apoptotic mechanism has been further refined. Two distinct pathways are involved in ATO-induced apoptosis depending on the p53 status of the cell. In MM cells with functional p53, ATO induces apoptosis through the intrinsic pathway involving release of caspase-9. In MM cells with mutated p53, apoptosis is triggered by the activation of caspase-8 and caspase-10[21].

ATO may also induce antitumor activity through an immunologic mechanism by increasing lymphokine-activated killer cells[22]. ATO also acts in the bone marrow microenvironment to decrease MM-cell binding to BMSCs and to inhibit IL-6 and VEGF secretion[23]. Another potential antitumor effect is via VEGF inhibition, although this has yet to be demonstrated in myeloma.

Results of 3 phase II studies using ATO, as a single agent in patients with relapsed MM refractory to conventional chemotherapy, have been reported[24-26]. Continuous and intermittent dosing schedules have been used. The combined results of the three trials showed only modest efficacy of ATO as a single agent in this group of patients, with only 2 of the 48 patients achieving greater than 50% reduction in paraprotein levels. Most of the responses were minor (12 of 48 patients, and a 25% to 49% reduction in paraprotein). Most patients experienced grade 3 or higher neutropenia and were unable to tolerate more than 2 months of treatment. It is also unclear from the published data as to what is the best dosing schedule; a continuous dosing is associated with a better response, but higher toxicity, while the intermittent dosing appears to be better tolerated, but produces poorer responses.

As a follow-up to their preclinical observation that ascorbic acid accentuated the activity of ATO, Bahils et al.[27] reported results from a small NCI-sponsored phase I study using ATO at 0.25 mg/kg per day plus 1,000 mg per day of ascorbic acid. This regimen appeared to be well tolerated and produced a response in 2 out of 6 refractory MM patients. Combinations with conventional therapies have also been tested. In one study, a combination of low-dose ATO (0.25 mg/kg twice weekly), oral melphalan, and intravenous ascorbic acid produced 4 responses in 10 relapsed patients[28]. In another study, a regimen combining ATO (0.25 mg/kg 5 days in week 1 and 2 times a week for weeks 2 to 10), dexamethasone, and ascorbic acid was used in 16 relapsed and/or refractory patients, and produced 1 solitary response. Overall, it seems that ATO would have limited efficacy in patients in whom multiple prior treatment has failed.

Farnesyltransferase inhibitors and lovastatin

Farnesyltransferase catalyzes the transfer of a farnesyl moiety to the cysteine terminal residue of substrate proteins. One of these substrate proteins is Ras, which is a signal transducer G-protein that requires prenyl lipid modification and membrane association for signal transduction[29]. The modification involves the covalent addition of either farnesyl or geranylgeranyl groups catalyzed by farnesyltransferase or geranylgeranyl transferase, respectively. The former process is inhibited by farnesyltransferase inhibitors (FTIs). Both processes are inhibited by lovastatin by inhibiting the production of mevalonate and depriving the cells of isoprenoids.

Ras is a valid target in MM as the ras gene is mutated in 39% of newly diagnosed MM, and is associated with a proper clinical outcome[30]. The percentage of patients with mutations increases to 81% at the time of relapse, making a ras mutation the most prevalent mutation in

MM[29]. Furthermore, IL-6 triggers myeloma cell growth via the Ras-dependent MAPK pathway.

Originally developed to block Ras activity, the antitumor effect of FTI is now believed to be mediated through other mechanisms, as the antitumor effect does not correlate with mutated Ras status[31]. Furthermore, Ras can also be prenylated by geranylgeranyl transferase; therefore, it is unlikely that Ras is the dominant target. The exact mechanism is still unclear at present.

Lovastatin is an attractive option for targeting Ras as it could potentially completely inhibit the isoprenylation process. In myeloma cell lines, lovastatin depleted membrane-localized Ras due to the inhibition of isoprenylation[32]. A more recent study showed that lovastatin induced apoptosis through inhibition of geranylgeranylation rather than farnesylation, possibly via regulation of Mcl-1, which is a critical survival factor for myeloma cells[33]. Lovastatin has been shown to overcome cell adhesion-mediated drug resistance in cell-line studies [34].

A phase II study in patients with relapsed or refractory myeloma using R11577 (tipifarnib) at 300 mg orally twice a day on a 3-weeks-on, 1-week-off schedule has been reported[35]. In this heavily pretreated population where more than 50% of enrolled patients failed previous high-dose chemotherapy and thalidomide, tipifarnib alone did not produce any objective responses, although 4 patients achieved a minimal response (defined as 25% to 49% decrease in serum paraprotein concentration) that persisted in 3, 7, 14 , and 26 cycles of treatment. However, disease stabilization (defined as 0% to 25% decrease in serum paraprotein concentration) was achieved in 64% of the 43 patients enrolled. The median time to progress from the start of treatment for these patients was 4 months (a range of 2 months to 26 months). The treatment was well tolerated, with fatigue being the most common complaint. Hematologic toxicity was not a significant problem. The dose used was also shown to be sufficient to inhibit the biochemical target farnesyltransferase, protein farnesylation, and oncogenic survival pathways[35].

Akt inhibition and recruitment of death receptors

Perifosine (Zentaris) is a synthetic novel alkylphospholipid. This is a member of a novel class of antitumor agents that interact with the cell membrane and modulate intracellular growth signal-transduction pathways. Perifosine induces significant cytotoxicity in MM cells triggered by c-Jun NH2-terminal kinase activation followed by caspase-8, caspase-9, and poly (ADPribose) polymerase cleavage, even in the presence of cytokines (ie, Interleukin-6 [IL-6] and insulin-like growth factor [IGF]-1) or bone marrow stromal cells (BMSCs). Specifically, it inhibits Akt/protein kinase B activity. Akt signaling is important for MM cell survival and antiapoptosis. A phase II trial of 25 patients treated with perifosine alone resulted in 24% stable disease. When combined with dexamethasone for progressive disease, 3 of 9 patients with evaluable disease had a minimal response, and an additional 2 patients had stable disease for an overall response rate of 55% in heavily pretreated MM patients[36]. Perifosine is also being studied in combination with bortezomib based on the synergistic effects observed in vitro.

Heat shock protein inhibitors

The heat shock proteins (HSP) are part of a ubiquitous chaperone complex that facilitates the proper folding, prevents misfolding or aggregation, and preserves the 3-dimensional conformation of a number of intracellular proteins. Preclinical studies of HSP90 inhibitors (eg, 17-allylamino-17-demethoxy-geldanamycin [17-AAG]) demonstrated antitumor effects. This agent suppressed proliferation and survival of MM cells both in vitro and in vivo. Clinical trials with HSP90 inhibitors have resulted in minimal activity as single agents, but more promising results have been observed when combined with the proteosome inhibitor bortezomib. A phase I/II trial combining tanespimycin plus bortezomib showed encouraging preliminary results: responses were seen in all dose levels in both bortezomib-naive (5/7 pts; 71%); bortezomib previously treated (5/13 pts; 38%), and bortezomib- refractory (2/6 pts; 33%) patients[37].

Bisphosphonates

Bisphosphonates are potent inhibitors of osteoclast-mediated bone resorption. They accumulate in the mineralized bone matrix, making it more resistant to dissolution by osteoclasts. Moreover, they directly inhibit the osteolytic activity of osteoclasts and reduce their survival. Thus, they represent the treatment of choice for hypercalcemia due to osteolytic lesions.

Pamidronate, a second generation amino-bisphosphonate, has been evaluated in a randomized, double-blind trial. Bone pain and analgesic requirement were significantly reduced in the pamidronate group. The total number of skeletal events and episodes of hypercalcemia were reduced by half. Survival was also prolonged in poor-prognostic patients who failed to respond to first-line chemotherapy before entering the trial. Thus, bisphosphonates are considered as a new form of treatment for MM. A more potent third-generation of bisphosphonates, such as zolendronate, has proven superior to pamidronate in the treatment of hypercalcemia and skeletal metastasis. However, preclinical studies have demonstrated a direct antitumor activity in human breast, prostate and myeloma cell lines. Large clinical studies are ongoing for breast and prostate cancers and MM. The results are expected to be presented this year.

Conclusions

Studies of bortezomib, thalidomide, and lenalidomide

have demonstrated promising activity in the treatment of relapsed/refractory and newly diagnosed multiple myeloma. Bortezomib alone and in combination is associated with high response rates and consistently high rates of CR, with a generally predictable and manageable toxicity profile. Substantial activity has also been seen with thalidomide-based regimens, notably thalidomide plus dexamethasone, in both advanced and newly diagnosed disease. The thalidomide analogue lenalidomide has shown activity in clinical trials, notably in combination with dexamethasone, and some aspects of its toxicity profile appear to be milder than with thalidomide. Monoclonal antibodies and other targeted therapies have been studied in recent years. Treatments involving these agents currently represent the most promising strategies for improving patient outcome, although no conclusions can be drawn from the available data regarding the most beneficial combinations, or the order in which these agents should be used in a patient's course of treatment. Further clinical investigations, including the results from ongoing phase III studies, should help establish the optimal use and sequence of these therapies for MM in the frontline and relapsed settings, and in combination with both conventional and investigational agents.

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