Review Article

Multiple Myeloma :
Recent Progress in Diagnosis and Treatment

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Multiple myeloma (MM) has been the most intractable hematological disease for many years. Recently, basic and clinical research has advanced remarkably and a new therapeutic strategy has been established. The introduction of high-dose melphalan with autologous stem-cell transplantation and the availability of molecular-targeted novel agents such as immunomodulatory drugs and proteasome inhibitors have dramatically changed the treatment strategies for MM. Achievement of a high response rate resulted in the extension of overall survival, but further research and the development of more multimodality therapeutic approaches is warranted to cure this disease. 〔*J Clin Exp Hematopathol 52(3)* : *149-159, 2012*〕

INTRODUCTION

Multiple myeloma (MM) is a neoplastic plasma-cell disorder, characterized by clonal proliferation of malignant plasma cells in the bone marrow, and monoclonal protein in the blood and/or urine, associated with organ dysfunction.[1] It accounts for approximately 1% of neoplastic diseases and is the second most common hematologic cancer. In Japan, the annual age-adjusted incidence is male/female : 2. 2/1. 7 cases per 100, 000 individuals and the median age at diagnosis is 66 years.[2] In the last 20 years, the introduction of high-dose melphalan with autologous stem-cell transplantation and the availability of molecular-targeted novel agents such as immunomodulatory drugs and proteasome inhibitors have dramatically changed the treatment strategies for MM. Achievement of a high response rate resulted in the extension of overall survival (OS).[3-5] In this review, recent progress in diagnosis and these novel agents for MM management are discussed.

PATHOGENESIS OF MM

MM has been considered to arise from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post-germinal-center B cells. Recent basic re-search has shown that multistep genetic and microenvironmental changes lead to the transformation of these cells into a malignant stage. MM is thought to evolve most commonly from a monoclonal gammopathy of undetermined clinical significance that progresses to smoldering myeloma and to symptomatic myeloma.[6] Several genetic abnormalities that occur in neoplastic plasma cells play major roles in the pathogenesis of myeloma.[7]

Two chromosomal translocation events are reported to be very important for the development of MM. First early chromosomal translocations occur at the immunoglobulin switch region on chromosome 14(q32.33), which is most commonly juxtaposed to MAF [t(14;16)(q32.33;23)] and MMSET on chromosome 4p16.3. After this event, the deregulation of two adjacent genes occurs, MMSET in all cases and FGFR3 in 30% of cases.[6,8] Second late-onset translocations and gene mutations that are implicated in disease progression include complex karyotypic abnormalities in MYC, the activation of KRAS and NRAS, mutations in FGFR3 and TP53, and the inactivation of CDKN2A and CDKN2C.[6,8] Other genetic abnormalities involve epigenetic dysregulation, such as alteration in microRNA expression and gene methylation modifications.[9] Gene-expression profiling enables us to classify MM into different subgroups on the basis of genetic abnormalities.[10]

Interactions between myeloma cells and bone marrow stromal cells or extracellular matrix proteins that are mediated through cell-surface receptors (e.g., integrins, cadherins, selectins, and cell-adhesion molecules) increase tumor growth, survival, migration, and also drug resistance. The adhesion of myeloma cells to hematopoietic and bone marrow stromal

cells induces the secretion of cytokines and growth factors, such as interleukin-6, insulin-like growth factor 1, vascular endothelial growth factor, members of the superfamily of tumor necrosis factor, transforming growth factor-β1, and interleukin-10. These cytokines and growth factors are produced and secreted mainly by bone marrow stromal cells and even by myeloma cells, and regulated by autocrine and paracrine loops.[11]

The adhesion of myeloma cells to extracellular matrix proteins (e.g., fibronectin, laminin, collagen, and vitronectin) triggers the up-regulation of cell-cycle regulatory proteins and anti-apoptotic proteins.[12] Bone lesions in MM are caused by an imbalance in the function of osteoblasts and osteoclasts. First, osteoblasts are suppressed by inhibition of the Wnt pathway, whereas the amplification of the RANK pathway and the action of macrophage inflammatory protein-1α activate osteoclasts.[13] The induction of proangiogenic molecules (e.g., vascular endothelial growth factor) enhances the microvascular density of bone marrow and accounts for the abnormal structure of myeloma feeding vessels.[12] These basic research findings have enabled us to develop several novel molecular-targeted drugs.

CLINICAL FEATURES OF MM

Diagnostic criteria

Several diagnostic criteria of MM have been proposed for almost half a century ; the most recent diagnostic criteria were proposed by the International Myeloma Working Group (IMWG). The IMWG criteria were based on simple diagnostic procedures and focused on the clinical importance. The diagnosis of myeloma is based on the presence of at least 10% clonal bone marrow plasma cells and monoclonal protein in serum and/or urine. In patients with true non-secretory myeloma, which accounts for about 2% of MM, the diagnosis is based on the presence of 30% monoclonal bone marrow plasma cells or a biopsy-proven plasmacytoma. MM is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue damage, including hypercalcemia (C), renal insufficiency (C), anemia (A), bone disease (B), and other myeloma-related symptoms (O), such as hyperviscosity syndrome and frequent infectious events, which are called the CRABO criteria (Table 1).[14,15]

IMWG recommends taking a detailed medical history and a physical examination, routine laboratory testing (complete blood count, chemical analysis, serum and urine protein electrophoresis with immunofixation, and quantification of monoclonal protein), and bone marrow examination (trephine biopsy plus aspirate for cytogenetic analysis or fluorescence in situ hybridization).[15,16] Conventional radiography of the systemic skeletal system remains the standard to identify myeloma-related bone lesions. Magnetic resonance imaging

Table 1. Criteria for diagnosis of myeloma
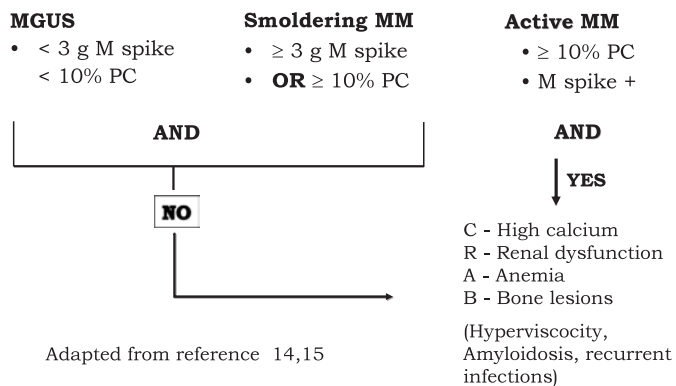
Adapted from reference 14,15

is recommended to evaluate symptoms in patients with normal results on conventional radiography and in all patients with radiographs suggesting the presence of solitary plasmacytoma of the bone. Computed tomography and magnetic resonance imaging are the procedures of choice to assess suspected cord compression and should be performed for urgent clinical management.[15,17]

Clinical staging system

Many clinical staging systems have been proposed in the past several decades, but many of these were too complicated and inconvenient in clinical practice. As a more useful staging system in a clinical context, IMWG proposed a new staging system, International Staging System (ISS), which defines three risk groups on the basis of serum β_2-microglobulin and albumin levels.[18] ISS is quite simple, but is very useful for prediction of the survival of patients in particular.

Cytogenetic analysis and risk group category

Cytogenetic analysis is quite important in MM. Specific translocations in the immunoglobulin heavy chain region that are detected on fluorescence in situ hybridization, such as t(4;14), deletion 17p13, and chromosome 1 abnormalities, are associated with a poor prognosis.[7] Recently, gene-expression profiling and gene copy-number alterations have shown a promising prognostic role.[16] High-risk disease and poor prognosis are defined by the presence of one of the following in each category : hypodiploidy, t(4;14), or deletion 17p13 ; high levels of β_2-microglobulin or lactate dehydrogenase ; and ISS stage III. Standard-risk disease is defined by the presence of hyperdiploidy or t(11;14), normal levels of β_2-microglobulin or lactate dehydrogenase, and ISS stage I.[16,18,19]

TREATMENT STRATEGIES

When to start active anti-myeloma therapy ?

In cases of symptomatic (active) MM, anti-myeloma therapy should be started immediately. Meanwhile, in cases of asymptomatic (smoldering) MM, the present therapeutic recommendation is only clinical observation, since early treatment with conventional chemotherapy has no impact on survival.[1,20,21] Since almost all MM are supposed to develop from monoclonal gammopathy of undetermined clinical significance, several investigational trials are currently underway to evaluate the ability of novel immunomodulatory drugs to delay the progression from asymptomatic to symptomatic myeloma.

Overview of treatment strategy

The historical perspective of the therapeutic strategies for MM is depicted in Fig. 1. Since the introduction of melphalan-prednisone combination therapy in the middle of the 20th century, a fairly old alkylating agent, melphalan, has been one of the most important drugs for myeloma treatment. From the 1970s to the 1990s, a new combination chemotherapy to improve the therapeutic efficacy of melphalan-prednisone further has been extensively evaluated, but failed to show any survival advantage. Apart from these combination chemotherapeutic approaches, the role of high-dose melphalan was extensively evaluated and showed significance not only in terms of a high response rate, but also a survival advantage. Initially, high-dose melphalan was supported by autologous bone marrow transplantation, but the introduction of peripheral blood stem cell transplantation (PBSCT) enabled high-dose melphalan to be administered more safely. Even with autologous PBSCT, high-dose melphalan therapy is a potentially risky strategy ; its indication needs careful consideration. In general, high-dose melphalan should be applied to patients under 65 years old to avoid severe treatment-related mortality.[22] In the case of older patients, combination chemotherapy has been the standard of care for a long time. The overall treatment algorithm is summarized in Fig. 2, showing that all active myeloma patients receive induction chemotherapy, followed by high-dose melphalan, or consolidation and/or maintenance therapy.

Introduction of novel agents and the mechanism of action

There is no doubt that combination chemotherapy and/or high-dose melphalan have improved the survival of MM patients, but almost all patients eventually relapsed and died ; no curative outcome was achieved for the disease. In 1999, a strong anti-angiogenic agent, thalidomide, was used for heavily treated refractory myeloma patients, resulting in a good response. After the success of thalidomide, several thalidomide analogs (lenalidomide and pomalidomide) were extensively developed and tested clinically. Since those thalidomide derivatives have more potent immunomodulatory effects rather than anti-angiogenic effects, those agents are called immunomodulatory drugs (iMIDs). Another novel molecular-targeted approach, proteasome inhibitor, was developed and showed very promising clinical results. In summary, novel anti-myeloma agents are currently categorized into two groups : one is proteasome inhibitors and the other is iMIDs (Table 2).

The anti-myeloma activities of proteasome inhibitors and iMIDs are summarized as follows :

1) Disruption of multiple signaling pathways that support the growth, proliferation, and survival of myeloma cells. Proteasome inhibition stimulates multiple apoptotic pathways, including the induction of the endoplasmic reticulum stress response, and through the inhibition of nuclear factor-κB signaling down-regulates angiogenesis factors, cytokine signaling, and cell adhesion in the microenvironment.[23]

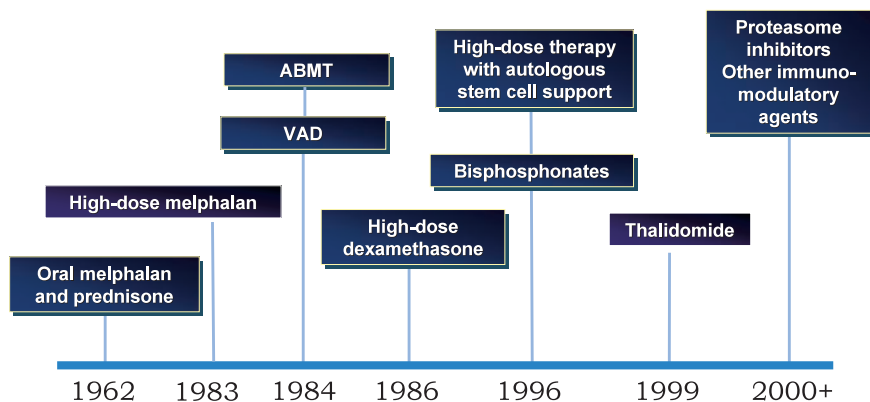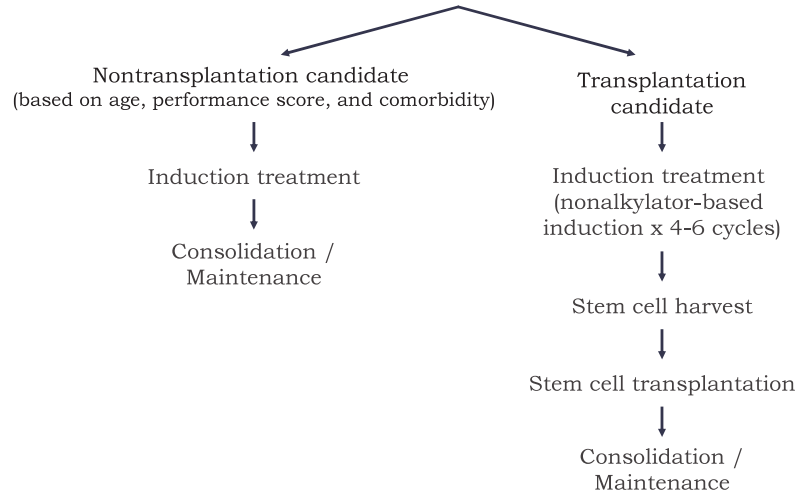2) iMIDs stimulate apoptosis and inhibit angiogenesis, adhesion, and cytokine circuits ; they also stimulate an

Fig. 1. Histological perspective of the treatment of multiple myeloma

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                    Nontransplantation candidate              Transplantation
              (based on age, performance score, and comorbidity)    candidate
                                ↓                                      ↓
                        Induction treatment                    Induction treatment
                                                              (nonalkylator-based
                                ↓                             induction x 4-6 cycles)
                         Consolidation /                             ↓
                          Maintenance                         Stem cell harvest
                                                                     ↓
                                                           Stem cell transplantation
                                                                     ↓
                                                              Consolidation /
                                                               Maintenance
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Fig. 2. Current treatment algorithm for untreated multiple myeloma

Table 2. Novel agents for multiple myeloma

· Proteasome inhibitor
  —Bortezomib
  —Carfilzomib
  —Ixazomib (MLN 9708)
  —Marizomib

· Immunomodulatory drug (iMIDs)
  —Thalidomide
  —Lenalidomide
  —Pomalidomide

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enhanced immune response to myeloma cells by T cells and natural killer cells in the host.[24] Among iMIDs, lenalidomide and pomalidomide have more potent immunomodulatory effects than thalidomide.

Current standard treatment algorithm for MM

After the introduction of proteasome inhibitors and iMIDs, the results of several clinical trials support the current standard care for newly diagnosed MM as follows :

1) The initiation of induction therapy with thalidomide, lenalidomide, or bortezomib plus hematopoietic stem-cell transplantation for patients under the age of 65 years who do not have substantial major organ (i.e., heart, lung, renal, or liver) damage.[25]

2) Autologous stem-cell transplantation with a reduced-dose melphalan (usually 100 mg/m^2) conditioning regimen should be considered for older patients or those with coexisting conditions.[26,27]

3) Conventional therapy combined with thalidomide, lenalidomide, or bortezomib should be administered in pa-

tients older than 65 years of age.[26]

4) Less intensive approaches that limit toxic effects or prevent treatment interruption that would reduce the intended treatment effect should be considered in patients over 75 years of age or in younger patients with coexisting conditions. Since a difference between biologic age and chronologic age is frequently experienced, the presence of coexisting conditions should determine the treatment of choice and drug dose adjustment.

5) Treatment strategies should include the use of induction regimens that are associated with high rates of good quality response, followed by consolidation and/or maintenance therapy. This multi-modality strategy would result in maximal tumor reduction. It has also been established that continuous treatment is essential in delaying myeloma cell regrowth.

It has been reported in several clinical trials that the level of response, in particular achievement of complete response (CR), is associated with an improvement of not only progression-free survival, but also OS. A complete response is defined as the elimination of detectable disease on routine testing.[14,15,28] More stringent criteria, such as the quantification of free immunoglobulin light chains in the serum,[29] the quantification of bone marrow myeloma cells on multiparameter flow cytometry, usually 4-color assay, and the identification of residual tumor cells on polymerase chain reaction assay, have been explored to define minimal residual disease, which is one of the most important independent prognostic factors for survival.[30,31] Younger patients who have a complete response after high-dose melphalan followed by autologous stem cell transplantation have prolonged progression-free survival (PFS), as well as OS.[32,33] In a retrospective analysis of 1,175 patients in 4 large-scale randomized trials, who received combination therapy with melphalan-prednisone and either bortezomib or thalidomide, patients

who had a CR had a 75% reduction in the risk of death after a median follow-up of 29 months, compared with those who only achieved very good partial response (VGPR) or less.[34] After 3 to 6 courses of induction therapy, 2 to 4 cycles of consolidation therapy and maintenance therapy with single agents until the time of disease progression have the potential to improve the PFS and OS. After high-dose melphalan therapy, consolidation therapy with bortezomib- or lenalidomide-based regimens significantly improved the rate of complete response, resulting in the prolongation of PFS and OS.[25,31]

Maintenance therapy with thalidomide, although limited by the occurrence of peripheral neuropathy,[35-39] or with the more recently available drug lenalidomide, improved PFS in younger and elderly patients.[40-42]

Recently, so-called risk-adopted stratification of treatment strategy according to the patient's risk factors has been reported. Although such individualized strategies have not been prospectively validated, some investigators have recommended the use of bortezomib-containing regimens for high-risk disease and lenalidomide- or thalidomide-containing regimens for standard-risk disease.[19,43,44] These recommendations are based on evidence that patients with t(4;14) who received combination therapy with lenalidomide and dexamethasone had shorter OS than those without t(4;14).[45] In contrast, bortezomib induction improved OS for patients with t(4;14), but not for those with deletion 17p13.[46] In the near future, risk-adopted therapy may become a standard of care. At present, among three novel agents, only bortezomib can be used as a first-line therapy in Japan.

Induction therapies in patients eligible for high-dose melphalan

The introduction of thalidomide, lenalidomide, or bortezomib into induction regimens has been effective to increase the rates of CR. In general, 3 to 6 cycles of induction therapy are recommended.[25] Combination therapy with dexamethasone plus thalidomide, bortezomib, or lenalidomide has been extensively used as an induction therapy before high-dose melphalan, resulting in CR of 8%, 15%, and 16%, respectively.[47-49] In a randomized study, combination therapy with bortezomib, thalidomide, and dexamethasone was superior to therapy with thalidomide plus dexamethasone with respect to both response rate and PFS.[50] Intermediate-dose melphalan (100 to 140 mg/m^2), followed by autologous stem-cell transplantation, can be used in patients between the ages of 65 and 70 years or in younger patients with coexisting conditions.[26,27]

OS is similar whether transplantation is performed at diagnosis or at the time of relapse, although early transplantation significantly prolongs PFS, as well as treatment-free interval and treatment-related toxic effects.[51]

A prospective clinical trial is now underway to evaluate the effect of delayed high-dose melphalan after induction with combinations containing three novel drugs.[52]

Induction therapies in patients not eligible for high-dose melphalan

A meta-analysis of studies involving 1,685 patients who were enrolled in six randomized studies comparing melphalan-prednisone with or without thalidomide showed that the addition of thalidomide increased median PFS by 5.4 months and OS by 6.6 months.[53] In a large, randomized study, combination therapy with melphalan-prednisone and bortezomib significantly increased the rate of CR, the time to progression, and OS, compared with melphalan-prednisone alone.[54,55] On the basis of these results, combination therapy with melphalan-prednisone plus either thalidomide or bortezomib is now considered the standard of care for patients who are not eligible for high-dose melphalan.

Another combination therapy, lenalidomide plus dexamethasone, increased the CR rate and PFS compared with high-dose dexamethasone alone.[56] In a randomized study comparing lenalidomide plus either low-dose or high-dose dexamethasone, the use of low-dose dexamethasone improved survival and reduced the frequency of serious adverse events.[49] Thus, lenalidomide plus low-dose dexamethasone is one of the standard regimens. A more intensive approach, a four-drug combination of bortezomib, melphalan, prednisone, and thalidomide, followed by maintenance therapy with bortezomib and thalidomide, was effective in elderly patients, with a 3-year PFS rate of 56%. To optimize treatment further, the dosing schedule for bortezomib was reduced from twice- to once-weekly infusions. The once-weekly schedule of bortezomib resulted in no disadvantage in terms of PFS with a considerably low risk of peripheral neuropathy.[57,58]

Consolidation and maintenance therapies

After induction therapy, consolidation therapy and maintenance therapy are now widely accepted, although no definitive guidelines are available. Consolidation with four courses of combination therapy with bortezomib, thalidomide, and dexamethasone after high-dose melphalan has been reported to increase the CR rate from 15% to 49%.[31] Several randomized studies have explored the role of thalidomide maintenance therapy after high-dose melphalan or conventional induction therapy. There was improvement in the rate of PFS, although the existence of a survival benefit was questionable. However, the risk of peripheral neuropathy after long-term thalidomide exposure limits its long-term use.[35-39] Lenalidomide may offer the same benefits with fewer toxic effects, and few cases of second cancers have been reported. In two independent French and American randomized studies

involving patients who had undergone high-dose melphalan, lenalidomide maintenance therapy decreased the risk of progression by 54% and 58% in comparison with no maintenance therapy.[40,41] In elderly patients who received combination therapy with melphalan, prednisone, and lenalidomide, lenalidomide maintenance therapy reduced the risk of progression by 75% in comparison with the risk among control subjects.[42] This benefit was evident in all categories of patients and was independent of the quality of response achieved after induction. Although the role of bortezomib plus an immunomodulatory drug in maintenance therapy remains to be elucidated, the results from two independent trials support this type of approach in elderly patients.[57,58] At present, lenalidomide appears to be the most suitable choice for maintenance. Recently, maintenance therapy with bortezomib was also evaluated in randomized studies and reported to be effective.[50,59] To date, no data are available to assess the potential risk of refractory relapse after maintenance therapy.

Single-center experience with novel drugs

1) Bortezomib

From 2007 to 2012, 98 patients with MM who had received at least one prior therapy were treated with the combination of bortezomib and dexamethasone (BD) in our hospital. Bortezomib (1.3 mg/m^2) and dexamethasone (20 mg) were administered by intravenous bolus injection on days 1, 4, 8, and 11 every 21 days. Oral dexamethasone (10 mg) was administered on days 2, 5, 9, and 12. Considering the oral dexamethasone dose in Japan and compliance with medication, we prescribe 10 mg of oral dexamethasone the day after injection. Acyclovir (200 mg once daily for two weeks in each cycle of BD therapy) was prescribed routinely to patients treated with BD for herpes zoster infection prophylaxis. BD therapy was continued until patients achieved the best possible response and entered the plateau phase. The plateau phase is defined as at least 3 months of clinical stability, with stable paraprotein levels (within ± 25%) regardless of the percentage decrement of M protein response as evaluated using the IMWG criteria.[28] Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 2). In principle, bortezomib dose was reduced or interrupted for grade 4 hematological toxicities and grade $\geq$ 3 non-hematological toxicities. When peripheral neuropathy (PN) was observed, bortezomib dose or infusion schedule was modified according to the following algorithm : bortezomib dose was reduced to 1.0 mg/m^2 for grade $\geq$ 1 with pain or grade 2 PN, interrupted until PN resolved with re-initiation at 0. 7 mg/m^2 per week for grade 2 with pain or grade 3 PN, and discontinued for grade 4 PN. As an alternative, bortezomib infusion was reduced to one a week (on days 1, 8, 15, and 22 every 28 days) for grade 1 PN with pain. If patients were eligible for transplantation, hematopoietic stem

cells were collected by the intravenous administration of VP-16 (500 mg/body ; day 1-2), followed by s.c. injection of granulocyte-colony-stimulating factor (250-300 μg/day) after about 4 cycles of BD. High-dose chemotherapy (L-PAM 100 mg/m^2 ; day 1-2) with autologous PBSCT was planned in patients who did not achieve VGPR with BD or relapsed after BD.

The patient characteristics are shown in Table 3. The median age of patients was 65 years old (range : 42-89). Patients had received prior treatments with dexamethasone alone, conventional chemotherapy, high-dose chemotherapy, thalidomide plus dexamethasone, and lenalidomide as indicated in Table 3. The median number of BD therapy courses to date was 6 (range 1-52) and the median follow-up time was 28 months (range : 1-60) in the surviving patients. The response data are summarized in Table 4. The overall response rate was 78.6%, including 10 cases (10.2%) of complete response (CR), 23 cases (23.5%) of VGPR, and 44 cases (44.9%) of partial response (Table 3). There were no differences between older patients ($\geq$ 65 y.o.) and younger patients (< 65 y. o.) in terms of the response rate. The probabilities

Table 3. Patients characteristics treated the bortezomib and dexamethazone (BD)

No. cases	98
Male/Female	50/48
Age : median (range)	65 (42-89)
PS (0/1/2/3)	19/41/21/15/2
Type of M-protein	
IgG/A/D/B-J	59/24/2/10/2
Plasmacytoma	1
Initial D-S (I/II/III)	7/36/55
Initial ISS (1/2/3)	30/51/17
Prior therapy	
Conventional CTx (+ Thal)	21 (6)
HDCTx (+ Thal)	17 (8)
DEXA + Thal	6
DEXA alone	53
Lenalidomide	3

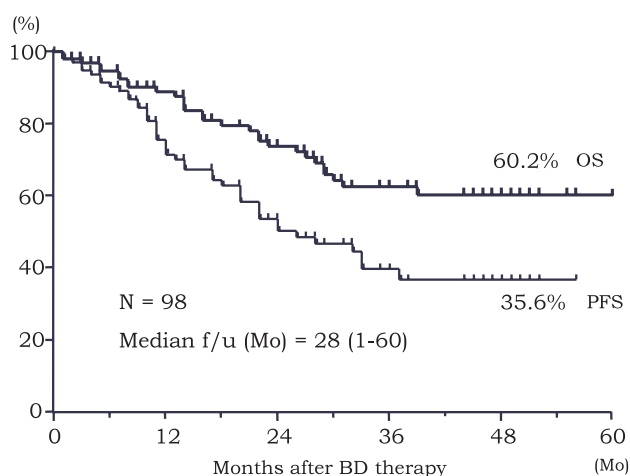**Table 4.** Response to the combination therapy of bortezomib and dexamethasone[*]

	total	< 65	> 66
No. case	**98**	**47**	**51**
No. course	6 (1-52)	4 (1-52)	5 (1-30)
CR	10 (10.2%)	7 (14.9%)	3 (5.9%)
VGPR	23 (23.5%)	10 (21.3%)	13 (25.5%)
PR	44 (44.9%)	17 (36.2%)	23 (45.1%)
SD	17 (17.3%)	5 (10.6%)	12 (23.5%)
PD	4 (4.1%)	3 (6.4%)	0

[*] : International Myeloma Working Group (IMWG) criteria

of OS and progression-free survival at 32 months were 60. 2% and 35. 6%, respectively (Fig. 3). Subgroup analysis according to the response to BD therapy showed that patients who achieved CR or VGPR tended to have longer survival than other patients (Fig. 4). Overall, BD therapy was well tolerated, and produced a significant response in relapsed or refractory MM patients.

2) Lenalidomide

Lenalidomide has been clinically available for the last 2 years. Because its indication is still limited to only relapsed/refractory MM in Japan, lenalidomide is used for most of the patients who relapse or are refractory to bortezomib in our

hospital. The patient characteristics are summarized in Table 5.

To date, 33 patients have been treated with the combination of lenalidomide and dexamethasone. The response rate of 30 evaluable patients is summarized in Table 6, with CR in 1 case (3.3%), VGPR in 4 cases (13.3%), partial response in 12 cases (40.0%), stable disease in 8 cases (26.7%), and PD in 5 cases (16.7%), indicating that lenalidomide can successfully rescue almost 60% of the patients who relapse or are refractory to bortezomib. On the basis of these results, we are now starting a new combination therapy trial to combine bortezomib and lenalidomide from the induction therapy to maintenance therapy.

Newly developed agents in basic research and clinical trials

As already mentioned, two major novel molecular-targeted agents for MM are proteasome inhibitors and iMIDs (Table 2). Second-generation drugs of each category have now been extensively developed and evaluated in both preclinical and clinical trials. Among newer proteasome inhibi-

Fig. 3. Overall and progression-free survival in the patients treated with the combination of bortezomib and dexamethasone in Niigata Cancer Center Hospital between November 2007 and March 2012
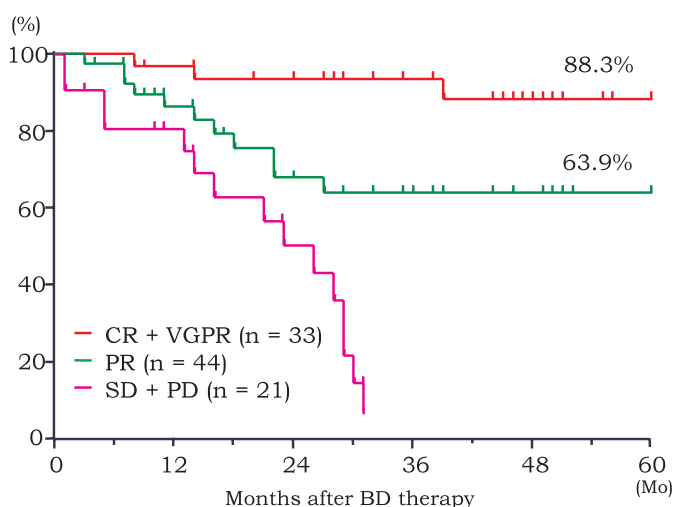
Fig. 4. Overall survival according to the response status after the combined bortezomib and dexamethasone therapy

Table 5. Patients characteristics treated with lenalidomide and deamethazone (LD)

No. cases	33
Male/Female	19/14
Age : median (range)	58 (42-84)
PS (0/1/2/3)	2/7/12/12
Type of M-protein	
IgG/A/D/B-J	18/8/2/5
Prior therapy	
Bortezomib	31
Conventional CTx (+ Thal)	10 (1)
High dose CTx (+ Thal)	5 (2)
DEXA + Thal	3
DEXA alone	15

Table 6. Response to combination therapy with lenalidomide and dexamethasone[*]

No. case	30
No. course	5 (2-10)
CR	1 (3.3%)
VGPR	4 (13.3%)
PR	12 (40.0%)
SD	8 (26.7%)
PD	5 (16.7%)

[*] : International Myeloma Working Group (IMWG) response criteria

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tors, carfilzomib is one of the most promising second-generation proteasome inhibitors ; it irreversibly inhibits protease activity and appears to have much greater and potent selectivity for the chymotrypsin-like proteases.[60] Compared with bortezomib, carfilzomib has minimal activity against off-target enzymes, which might result in less adverse drug reactions in a clinical context. In the clinical development of second-generation proteasome inhibitors, carfilzomib has been investigated most extensively for clinical activity and adverse events.[61] Ixazomib (MNL9708) is another boronate proteasome inhibitor that reversibly inhibits primarily the chymotrypsin-like activity of 20S proteasome. Compared with the same boronate proteasome inhibitor, bortezomib, ixazomib has a shorter dissociation half-life and has demonstrated greater tissue penetration in pre-clinical evaluation. Furthermore, ixazomib is not only intravenous, but also orally available and is the first oral proteasome inhibitor to enter clinical trials in MM.[62] Marizomib (NPI-052) is a natural lactone compound derived from the marine bacterium *Salinispora tropica*. Marizomib is an irreversible proteasome inhibitor, which inhibits both chymotrypsin-like and trypsin-like protease activities, but has almost no activity against caspase-like protease. Because of these unique characteristics, marizomib has a unique efficacy and safety profile and does not exhibit cross-resistance with other proteasome

inhibitors.[63] In Japan, phase I/II clinical trials of both carilzomib and ixazomib are now underway.

As a third- rather than a second-generation iMID, pomalidomide has been developed and evaluated for its *ex vivo* and clinical activity. Pomalidomide is one of the two thalidomide analogues, the other one being lenalidomide. Compared with lenalidomide, pomalidomide possesses strong immunomodulatory activity, as well as anti-angiogenic activity.[64,65] A phase I/II trial is now underway to evaluate its clinical activity and toxic profiles in Japan.

Since biological research has progressed markedly in the field of MM, several mechanisms and pathways that determine how MM grows have now been reported in detail (Fig. 5).[12,66,67] Each pathway and mechanism is very important to develop other novel molecular-targeted therapeutic strategies, and, in fact, quite a few new agents have been developed and tested in clinical trials. Most of these new agents are tested for clinical activity in combination with proteasome inhibitors and/or iMIDs (Table 7).

CONCLUSIONS AND FUTURE DIRECTIONS

In the last 10 years, the introduction of thalidomide, lenalidomide, and bortezomib has changed the treatment paradigm and prolonged the survival of patients with MM. Even with
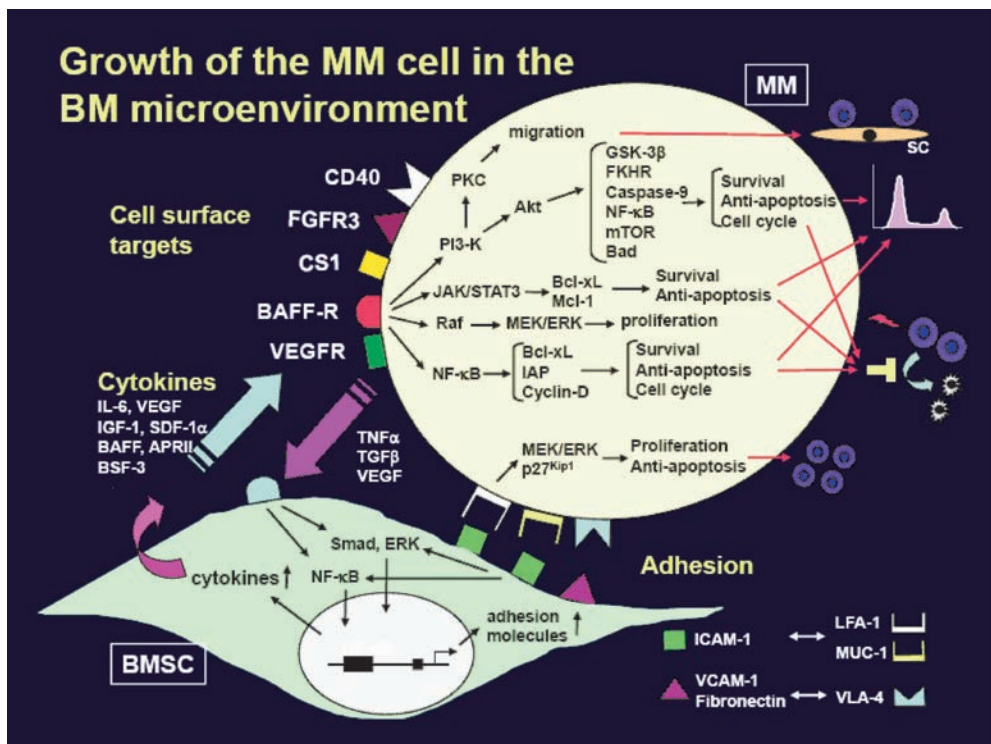

Fig. 5. Present understanding of the growth of myeloma cells in the bone marrow microenvironment (adapted from references 12, 66, and 67)

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Table 7. Examples of targeted therapy now in clinical development

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- ・P13K/mTOR/AKT pathway inhibitors
- ・KSP inhibitors
- ・Aurora and other kinase inhibitors
- ・HDAC inhibitors
- ・HSP90 inhibitors
- ・Moab IL-6R, CS1, CD138
- ・FGFR3 inhibitors
- ・Other

Alone or with Bortezomib, Lenalidomide

the utilization of these novel agents, high-dose melphalan still remains the standard care for younger patients eligible for high-dose therapy.

Combination therapy with melphalan-prednisone plus either thalidomide or bortezomib is considered to be the standard care for patients who are not eligible for high-dose melphalan, but, at present, bortezomib is the only choice as a first-line drug in Japan. Consolidation/maintenance therapy with thalidomide or lenalidomide improves PFS, but longer follow-up is needed to assess the effect on OS. Second- or even third-generation proteasome inhibitors and iMIDs, or several other promising novel molecular-targeted agents, have been extensively developed and tested in clinical trials, indicating that careful and prospective development of multimodality therapeutic strategies is warranted for the cure of intractable multiple myeloma.

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