## Induction therapy for newly diagnosed multiple myeloma (NDMM)

Effect of novel agents on outcome in NDMM was dramatically improved (Fig. 2) [7]. Using the combination therapies with new drugs, multiple myeloma (MM) is changing from a incurable disease into either a chronic one or a curable disease.

### Bortezomib

Bortezomib IV is an ubiquitin-proteasome inhibitor and indicated for the treatment of MM. Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. It is cytotoxic to a variety of cancer cell types in vitro and causes suppression in tumor growth in vivo in nonclinical tumor models, including MM. Specifically, bortezomib is effective in MM via its inhibition of nuclear factor-$\kappa$B activation, its attenuation of interleukin-6-mediated cell growth, a direct apoptotic effect, and possibly antiangiogenic and other effects [8]. Regarding the treatment of patients who are not eligible for transplantation, MPT and MPB have shown significantly better overall survival (OS) benefit than that of MP and are the recommended treatments [6, 9]. The proteasome inhibitor bortezomib has been approved in the USA in 2005 for the treatment of MM patients with a history of at least one prior therapy, based on results from the phase III APEX study which showed superiority of bortezomib over high-dose dexamethasone in patients with relapsed MM [10]. The majority of treatment guidelines currently recommend incorporating HDT/SCT into initial therapy programs for patients who are 65 years of age or younger and to consider such a therapy for patients 60–70 years of age with good performance status and a lack of co morbid illnesses since HDT/SCT provides the highest chance of inducing a complete remission. However, even when patients achieve CR, the vast majority of patients will ultimately relapse. The standard frontline therapy for patients who are 65 years of age or older, and for patients who are not likely to proceed to HDT/SCT, consists of oral MP at doses similar to those used in this study. Combination therapies such as MP (at a dose of 0.25 mg/kg/day) are given orally at doses used for 4 consecutive days every 6 weeks, showed superior survival versus melphalan alone. With MP therapy, an OR rate of approximately 50 %, a CR rate of 2 to 5 % and a median time to response of 3–5 months have been historically reported [4].

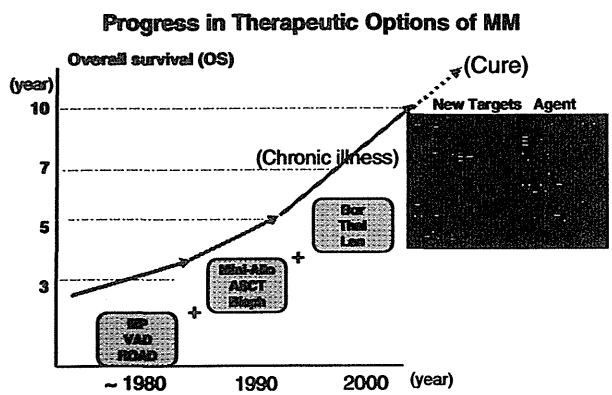



Fig. 2 Effect of novel agents on outcome in newly diagnosed myeloma. Overall survivals were elongated by the effect of HDT with ASCT from 1994, longer due to new drugs from 2001. 1970, MP; 1986, HDT with ASCT; 1999–2000, new drugs (bortezomib, lenalidomide, and thalidomide) were epoch making. The CS-1 antibody (elotuzumab) and IL-6 antibody (siltuximab) may be effective with some combinations. Bendamustine, a bifunctional agent, shares properties of alkylating agents and purine analogs. New combination trials of new agents, as shown in right-side may be promising

### Final results of the phase 3 VISTA trial

Recently 5 year OS follow up data has been published. The data indicates that OS in MPB with 60.1 months follow-up is significantly superior to that of MP. The OS of MP-B and MP were 56.4 months (13.3 months improvement) and 43.1 months respectively. This data is very much remarkable because the OS improvement was 13.3 months although even MPT could improve only 6.6 months in its meta analysis. As a result of this VISTA study, MPB became the standard treatment for untreated transplant in-eligible patients [11].

To evaluate safety, pharmacokinetics (PK) and efficacy of bortezomib combined with melphalan and prednisolone (MPB) therapy, we conducted a phase I/II study for untreated Japanese MM patients who were ineligible for hematopoietic stem cell transplant (HSCT). This was a dose-escalation study designed to determine the recommended dose (RD) of bortezomib in combination with melphalan and prednisolone by evaluation of the maximum tolerated dose based on dose-limiting toxicity (DLT) in the phase I portion, and to investigate the overall response rate (ORR; CR + PR) and safety of MPB therapy in the phase II portion. Particularly, a continuity of treatment cycles was historically compared with a global phase III study (VISTA trial), and the incidence of interstitial lung disease was assessed. This phase I/II study in Japan suggests that the RD of bortezomib in MPB therapy is 1.3 mg/m$^2$ and the MPB therapy in newly diagnosed Japanese MM patients ineligible for HSCT is as effective as that shown in VISTA trial. Further investigation is necessary to confirm the appropriate administration schedule of this combination in Japanese patients [12].

**International uniform response criteria**

| | PR | VGPR | nCR | CR | sCR |
|---|---|---|---|---|---|
| Serum Protein Electrophoresis | ≧50% | ≧90% | 0 | 0 | 0 |
| Urine Protein Electrophoresis | ≧90% | < 100mg/24h | 0 | 0 | 0 |
| Bone Marrow Plasma Cells | — | — | <5% | <5% | <5% |
| Bone Marrow Immunofluorescence | — | — | — | — | Negative |
| Serum/Urine Immunofixation | — | — | Positive | Negative | Negative |
| Serum Free Light Chain Ratio | — | — | — | — | Normal |

Durie BGM, et al. Leukemia 20:1467-73, 2006.

**Fig. 3** International uniform response criteria. Serum protein electrophoresis, serum/urine immunofixation, and serum free light chain ratio are important

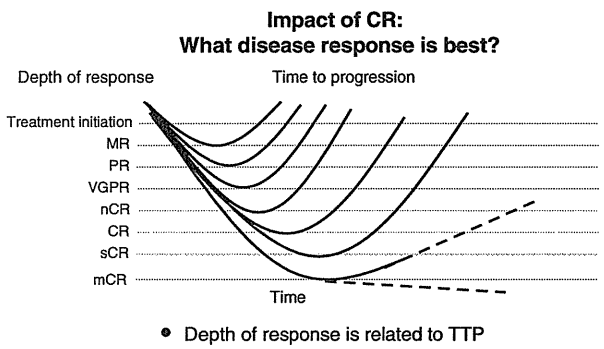



**Fig. 4** Impact of CR: depth of response is related to TTP. CR is the surrogated marker for the long survival

What should be the goal of treatment in multiple myeloma? If cure is the goal, then CR is the critical first step (Fig. 3) [13]. CR is a treatment goal in many hematological malignancies, eg- AML, ALL and lymphomas. In the past, achievement of CR in MM was rare. New treatments can increase the rate of CR to the similar level with high-dose therapy followed by ASCT (Fig. 4) [14–16]. Also, CR rate in Phase 3 trials in non-transplant patients was: MPB 30 %; MPT 2-16 %; MPR 13 %; MPR-R 18 %, and long term RD 22 %. MM may not be a single disease cytogenetically; achievement of CR seems particularly important in the 15 % of patients with high-risk MM, since survival is similar in patients without high-risk features who have and have not achieved CR [6, 17–20].

## Cyclophosphamide and thalidomide

Cyclophosphamide has been added to thalidomide and dexamethasone (CTD) with excellent response rates among newly diagnosed MM patients who received subsequent SCT, with higher response rates seen after SCT.

The combination in 3-weekly schedules of cyclophosphamide (50 mg PO or 300 mg/m$^2$ PO weekly or 150 mg/m$^2$ d1–5), thalidomide (200–800 mg daily, increasing doses or intermittent administration 400 mg d1–5 and d14–18) and dexamethasone (40 mg per day for 4 days) (CTD) results in an ORR of around 60 %, a median TTP of 10–12 months and a 2-years PFS of 57 % [21–23].

Comprehensive reviews on the use of thalidomide have been published and include efficacy and safety in relapsed MM. The rationale for using thalidomide was based on its antiangiogenic properties because, in MM, increased microvessel density has been inversely correlated to survival. However, thalidomide has multiple modes of action, including immunomodulatory effects. This initial experience generated a great enthusiasm, and a large number of phase II trials were rapidly conducted. A systematic review of such 42 trials on >1600 patients confirm that the response rate is 29 % with an estimated 1-year overall survival (OS) of 60 %. The well-known teratogenicity of thalidomide is not a major concern in patients with MM because of patients age, but justifies careful informing of patients and programs to avoid drug exposure in women with childbearing potential. The major toxicities of thalidomide are fatigue, somnolence, constipation, and mostly peripheral neuropathy, which are related to the daily dosage and to treatment duration. The overall incidence of peripheral neuropathy is 30 % but may be higher if treatment is prolonged for >1 year. Because this complication may be disabling and sometimes irreversible, patients should decrease the dose or stop the treatment if significant numbness occurs.

After induction treatment, two to four cycles of combination therapies is followed by the maintenance therapy, which is continuous therapy with a single agent, with reasonable balance between maximum benefits and minimum toxicities [24] until the time of disease progression.

## Maintenance therapy for multiple myeloma

I prefer disease control as a treatment goal, except in selected high-risk patients in whom an aggressive approach to achieving CR may be the only option to long-term survival (Fig. 5). The disease control approach involves targeting very good partial response (minimal residual disease) rather than CR as a goal by using limited, less intense therapy first and moving to more aggressive approaches as need arises (sequential approach): this allows patients to help determine the timing and number of transplants.

Post-transplant consolidation/maintenance with novel agents can become an important step forward. Thus, it has recently been reported that post-transplant consolidation with thalidomide, lenalidomide or bortezomib increases the CR rate. In this regard, it has been shown that post-ASCT consolidation with VTD can induce long-lasting molecular remission [25, 26]. Thalidomide maintenance prolonged the OS in two transplant series [27].

The response rate to treatment with single-agent thalidomide in patients with relapsed and/or refractory MM is between 30 and 40 % [28].The response rate increases from 50 to 65 % when thalidomide is combined with dexamethasone with or without cytotoxic agents.

The cure-versus-control debate is hot. Indeed, CR is a surrogate marker for improved OS. However, for the majorities of MM patients, the disease control approach (Maintenance therapy) involves targeting very good partial response (VGPR) rather than CR as a goal. This is a pilot study of the prospective, sequential registered trial of the

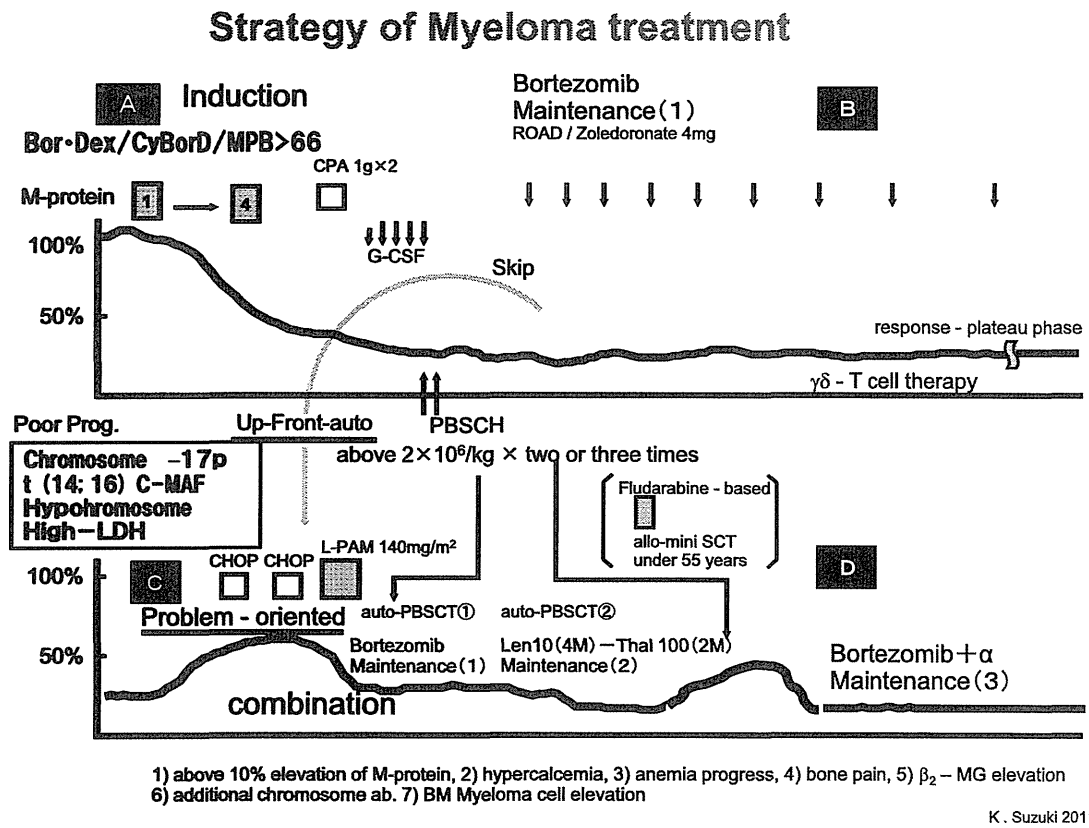



**Fig. 5** Strategy of myeloma treatment in our institute. We divided in four phases: initial therapy by two to four courses of BorDex/ CyBorD/ or MPB >66 years old followed by PBSC-harvest. If the high risk patients, up-front PBSC-transplantation followed by Bor-maintenance. Otherwise, if the standard risks patients, maintenance-therapies may be the B-stages until progress disease. PD are defined as (1) above 10 % elevation of M-protein, (2) hypercalcemia, (3) anemia progress, (4) bone pain, (5) $\beta_2$-MG elevation (6) additional chromosome ab. (7) BM myeloma cell elevation. After PD, problem-oriented PBSCT may be done with second maintenance with Lenalidomide

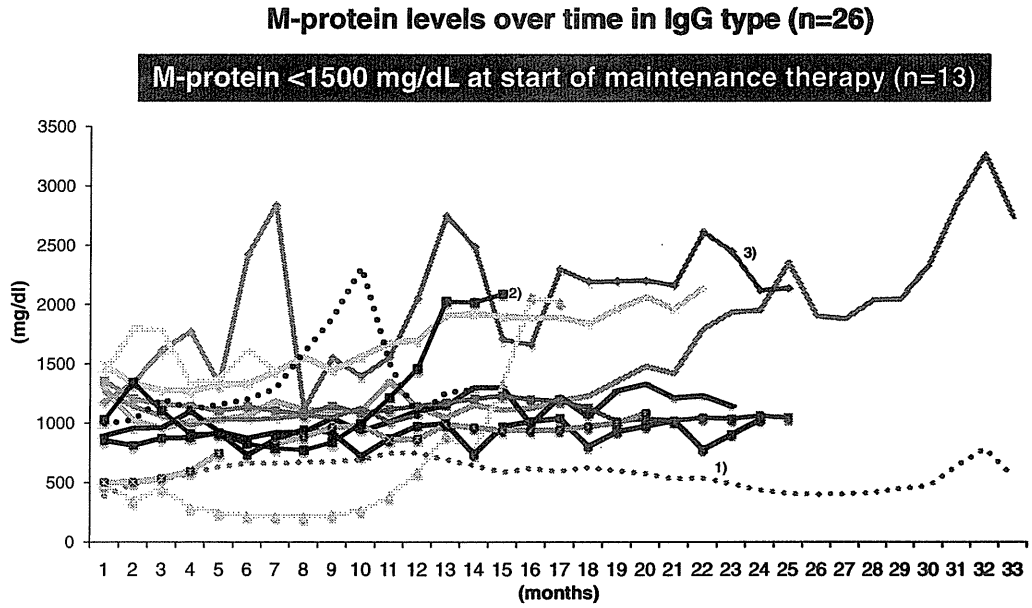
significance of BD maintenance therapy for long-term survival with good QoL.

From September 2008, we continued exploratory study of effects of bortezomib on the ability of patients with relapsed, refractory multiple myeloma to continue maintenance therapy [29] (Clin. Eth. No: JRC 170). Bortezomib had been associated with fatal lung disorders, with a high number of reported cases in Japan. Post-marketing surveillance, however, showed a low incidence of 3.6 %. Peripheral neuropathy (20–30 %) is a major concern. Informed consent was obtained from 43 patients with a mean prior treatment (e.g., VAD, ROAD, ASCT) history of 23 months, PS $\leq$2, and no significant organ lesions. Efficacy of bortezomib as maintenance therapy in patients achieving VGPR/PR with remission induction therapy has not been investigated. This study of bortezomib maintenance therapy in patients achieving VGPR/PR with bortezomib is therefore investigating the effects of treatment on patients ability to continue maintenance therapy and adverse drug reaction incidence. There were 11 cases of karyotypic abnormalities (35 %) with 8 cases of complex abnormalities. Patients received dexamethasone (20 mg/body) daily for 2 days every 2 or 4 weeks with bortezomib, 1.3 mg/m$^2$ div. Time-to-progression (TTP) was the primary efficacy endpoint (Fig. 6) [29]. The adverse reactions of BD maintenance include asthenia conditions, peripheral neuropathy, thrombocytopenia were all G-1 and well tolerated. Long-term survival with good QoL is the most important goal for the elderly/low genetic risk MM patients. BD maintenance is good available for this group (24/43 cases) over 20 months (Fig. 7), especially in the cases of total delivery dose over 40 mg. However, the other group of patients (8/33 cases) in rapidly relapsing with complex karyotypic abnormalities may need the strong combination chemotherapy.

Recently, lenalidomide maintenance therapy improved median progression-free survival (41 vs. 23 months with placebo; hazard ratio, 0.50; $P < 0.001$) [30].

## Therapy for relapsed or refractory multiple myeloma (RRMM)

Progressive disease is defined as follows: (1) Above 25 % elevation of M-protein, (2) hypercalcemia: corrected serum calcium >11.5 mg/dL, (3) the absolute increase of free light chain (FLC) must be >10 mg/dL, (4) definite development of new bone lesions or soft tissue plasmacytomas, (5) decrease in hemoglobin of >2 g/dL, (6) rise in serum creatinine by 2 mg/dL or more, (7) increase of BM myeloma cell above 10 %.




1) 46,XX,t(11;14)(q13;q32)[1]/46,XX[29] 2) 50,add(X)(q28),-X,-1,+3,+7,-8,+9,+15,del(22)(q139,+3mar,inc[cp12]/46,XX[18]
3) 83~85,XX,-X,-X,der(1;2)(q10;q10)- 2,-2,-2,-3,add(3)(p2?),-4,-4,add(4)(p16),add(4)(p16),-5,-5,-6,-6,-8,add(10)(q22)2,-13,-13,-13,del(13)(q?),- 14,-15,-16,-16,-16,-17,add(18)(q23)×2,+14 ~ 15mar,inc[cp2]/

**Fig. 6** Maintenance therapy with bortezomib for the VGPR IgG-myeloma patients. Monthly administration of bortezomib are effective as the stabilization of M-protein levels over time in IgG type ($n = 26$). It needs 20 months average until PD. However, high risk group are difficult to control in this manner

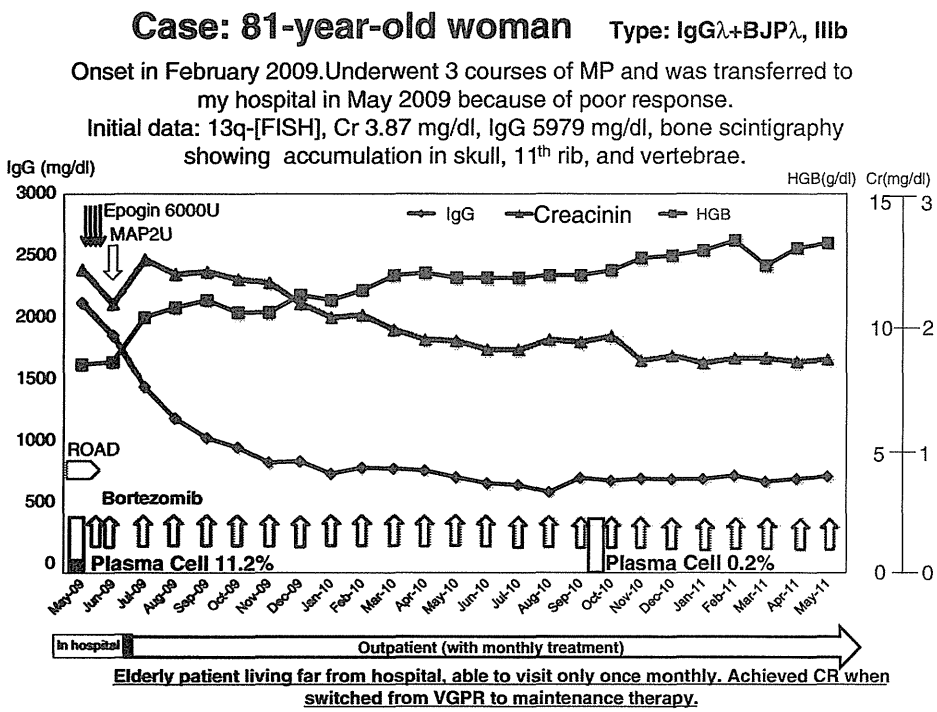



**Fig. 7** A case of Bor-maintenance therapy. Elderly patient (81 year old female: IgGλ + BJPλ, stage IIIb) living far from hospital, can visit only once monthly. After 14 months therapy, she achieved CR when switched from VGPR to maintenance therapy

## Analysis of second primary malignancies (SPM)

Another important issue in MM is risk of developing SPMs due to living longer from diagnosis. Population studies show MM patients have increased risk of specific SPMs following initial diagnosis, notably acute myeloid leukemia (AML). Some MM therapeutic agents are particularly associated with elevated risk of SPMs. Melphalan is associated with increased risk of secondary acute leukemia. There were imbalances in SPM incidence, including myeloid and lymphoid leukemias, with post-transplant lenalidomide maintenance therapy and with MP-lenalidomide. Persistent significant OS benefit with VMP versus MP; 13.3-months increase in median, and MPT versus MP increase 6.6 months [9].

Secondary malignancies and lenalidomide: by summarizing the data to-date, the incidence of all/invasive SPM is significantly increased in Lenalidomide arms, driven by hematologic SPM ($P < 0.001$). B-ALL, Hodgkin lymphoma is reported in post high-dose melphalan and ASCT setting. Sensitivity analysis (including SPM as an event) demonstrates negligible PFS differences. The overall benefit–risk profile of lenalidomide in NDMM remains positive [31, 32]. Risk Factors for Secondary Malignancies Treatment with lenalidomide may be treatment duration >24 months, male, age >55 years, ISS stage III, previous DCEP (role of concomittant or previous exposure to alkylators?) induction by univariate and multivariate analysis in IFM 2005.

In Japanese SPM Report by JRCMC, retrospective analysis for 325 MM patients from 1998 to 2010 (13 years) showed t-MDS/AML developed 17 (5.2 %) patients. Median time to onset: 52 months in t-AML and months in t-MDS. All the patients with t-AML died in a short time, suspected to be treated with Melphalan, and no patients had been given Lenalidomide. We have to select chemo regimen taking into account the risk of t-MDS/AML [33].

## Renal dysfunction in multiple myeloma

Timing of treatment initiation in multiple myeloma is depending on existence of organ dysfunction. Usually when any symptom such as bone symptoms, renal dysfunction, anemia, or hypercalcemia is observed, it is diagnosed as symptomatic multiple myeloma and treatment should be started. Renal dysfunction in multiple myeloma is one of the complications that require the most careful attention and occurs via various mechanisms. Of these, the most frequent case is cast nephropathy, also known as myeloma kidney, in which excessive light chains of M protein (BJP) secreted by proliferated plasma cells form cast by depositing themselves in renal tubules. In addition, hypercalcemia associated with osteolysis by myeloma cells, deposition of amyloid in glomeruli, hyperviscosity syndrome, hyperphosphatemia, renal infiltration of myeloma cells are also the causes of renal dysfunction. Other than those, care must be given to recurring urinary tract infection, drugs, dehydration that may act as exacerbation

factor. According to the statistics of Japanese Society of Myeloma [34], approximately 15 % of newly diagnosed multiple myeloma patients have complication of renal dysfunction and the rate increases as the disease progresses. Bence Jones protein (BJP) type and IgD type of myeloma that excrete high amount of Bence Jones protein into urine show high frequency of renal dysfunction. In 197 patients diagnosed as multiple myeloma during 12 years (1995–2006) in our facility, 3.6 % of IgG type and 8.9 % of IgA type showed higher than 2 mg/dL of creatinine on the first visit, were whereas BJP type accounted for 36.8 % (Fig. 8). Because renal dysfunction becomes irreversible if timing of treatment is missed, immediate treatment is necessary. It is reported that renal dysfunction remains reversible when serum creatinine is below 4 mg/dL, Ca is below 11.5 mg/dL and urine protein is 1 g/day or lower [35]. Although these are the data before introduction of novel agents, in the 423 patients with newly diagnosed multiple myeloma, patients with renal dysfunction (22 %) showed significantly shorter survival time compared to the patients with normal renal function (8.6 vs. 34.5 months). In addition, Blade et al. reported that in the same patients with reduced renal function, those who recovered their renal function by subsequent chemotherapy showed significantly extended survival time compared to those without recovery of renal function (28.3 vs. 3.8 months). Therefore, although renal dysfunction in multiple myeloma is a poor prognostic factor, good prognosis can be expected if the treatment restores renal function. For this, it is important to restore renal function by implementing effective treatment in patients with renal dysfunction before it becomes irreversible and requires hemodialysis. In the multiple myeloma patents in our facility mentioned above, hemodialysis was introduced to eight out of 197 cases.

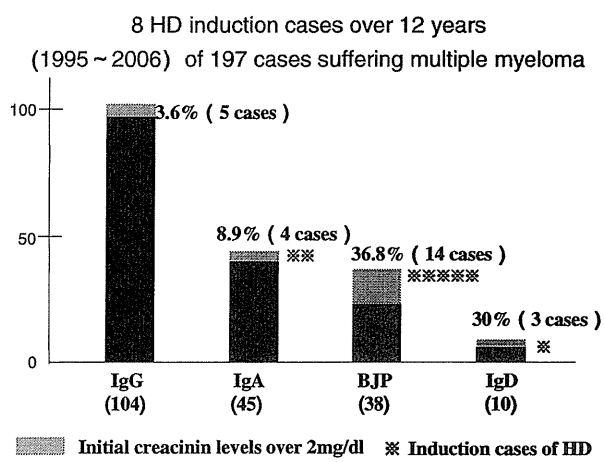



**Fig. 8** HD induction cases suffering MM. Initial creatinine levels over 2 mg/dL were 10–20 %, mainly in BJP and IgD type. HD induction was also frequent in these populations

## Improvement of renal function and treatment strategy for multiple myeloma

Improvement of the primary disease is the basic remedy of renal dysfunction that complicates with multiple myeloma. Since 2005, treatment strategy for multiple myeloma has significantly changed due to the successive introduction of novel agents. The three drugs including a proteasome inhibitor bortezomib, and two immunomodulatory drugs (IMiDs), lenalidomide and thalidomide, are referred to as novel agents, and each drug has characteristic profiles of efficacy and safety. While all those agents can be expected to restore renal function due to improvement of the primary disease, bortezomib, with strong antitumor effect, is reported to rapidly improve renal function (Fig. 9). Roussou et al. retrospectively compared improvement of renal function among traditional chemotherapy group, IMiDs (lenalidomide or thalidomide)-based treatment group, and bortezomib-based treatment group with 96 cases of newly diagnosed multiple myeloma. It showed that the best and the most rapid improvement of renal function were observed in the bortezomib-based treatment group. Renal response rate (minor response and better) based on creatine clearance improvement and time to response as 59 % and 1.8 months in chemotherapy group, 79 % and 1.6 months in IMiDs-based group, and 94 % and 0.69 month in bortezomib-based group, respectively [36]. In addition, some cases with withdrawal from dialysis are also reported. Thus, administration of bortezomib should be considered in patients with acute or severe renal dysfunction if it is possible.

## Lenalidomide

Lenalidomide is an anti-myeloma drug possessing dual functions of antitumor effect and immunomodulating activity. Because lenalidomide is urinary excreted, its blood concentration increases in patients with renal dysfunction which leads to high incidence risk of adverse reactions [37]. However, lenalidomide itself has no renal toxicity and clinical studies showed improvement of renal function in the patients treated with lenalidomide. Lenalidomide can be administrated by proper adjustment of its dose corresponding to renal function according to the package description [38]. In fact, it is reported that adjusted dosing of lenalidomide to patients with renal dysfunction resulted with similar anti-myeloma efficacy to those with normal renal function [39, 40], and recovery of renal function was also observed [41]. Similar to bortezomib, cases that withdrew from dialysis are reported [42].

| Renal Response | CC-based regimen ( n=32 ) | IMiDs-basede regimen ( n=47 ) | Bortezomib-based regimen ( n=17 ) |
|---|---|---|---|
| CR renal | 41% | 45% | 71% |
| | 47% | 45% | 82% |
| ≧MR renal | 59% | 79% | 94% |
| Time to Response | 1.8 months | 1.6 months | 0.69 months |

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| Stages | | GFR (ml/min/1.73 m²) |
|---|---|---|
| 1 | Kidney damage with normal or elevated GFR | Over 90 |
| 2 | Kidney damage with mild reduction of GFR | 60-89 |
| 3 | Moderate reduction of GFR | 30-59 |
| 4 | Severe reduction of GFR | 15-29 |
| 5 | Renal failure | Below or Hemo Dialysis |

| Response | Baseline eGFR (ml/min/1.73 m²) | Best CrCl Response (ml/min)※ |
|---|---|---|
| CR renal | <50 | ≥60 |
| PR renal | <15 | 30-59 |
| MR renal | <15 | 15-29 |
| | 15-29 | 30-59 |

※At least keep 2 months

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**Fig. 9** Complete response (CR) renal. CR may be attained by bortezomib-based regimen not only the high levels percentage but also time to response. 5-stage is divided as the figure

Stratified analysis of lenalidomide/dexamethasone therapy by age showed similar efficacy and tolerability in elderly (over 65 years of age) to those of youth [43]. Hence this therapy is considered to be useful especially for elderly patients with renal dysfunction if the dose is properly adjusted corresponding to the renal function. Thalidomide does not require dose control depending on renal dysfunction, but it has not been reported in large studies that thalidomide is effective on the improvement of renal function. In any case, early diagnosis and timing of initiation of treatment are important. In addition, full understanding of efficacy and safety profiles of novel agents and using them in combination with existing drugs appropriate for individual patients are the basis of treatment strategy.

## Diagnosis of AL amyloidosis and renal dysfunction

AL amyloidosis is a disease with poor progression in which deposition of amyloid causes multiple organ failure. Amyloid consists of immunoglobulin light chains secreted from monoclonal proliferated plasma cells. Its relative disease MM is often complicated with AL amyloidosis. In spite of the fact that it has the same chromosome translocation such as t (11:14) to MM, it shows different pathological condition (Fig. 10). This may be due to slight difference of translocation breakpoint between AL amyloidosis and MM. However, the disease mechanism remains unknown.

It is classified to cardiac, renal, gastrointestinal, and pulmonary amyloidosis depending on the main organ with amyloid deposition. The symptoms vary and the most common cause of death is cardiac failure. The diagnosis is based on confirmation of amyloid deposition in the involved organs. When AL amyloidosis is suspected in patients with clinical findings such as general malaise, edema, heart failure, tubercle in margin of tongue, and skin nodule with stigma, biopsy of organs should be first conducted to confirm deposit of amyloid (Fig. 11). Amyloid is positive with Congo red stain and has positive signal under polarized light with the polarizing filters. AL amyloidosis is definitely diagnosed by confirming monoclonal proliferation of plasma cells through identification of M protein and/or staining pattern of cell surface antigens in addition to deposition of amyloid. Low detection sensitivity of M protein even in immunofixation in AL amyloidosis has been a problem so far. However, the free light chain (FLC) assay that has listed itself in insurance coverage in 2011 in Japan, allows over 90 % detection and is reported to be effective in diagnosis. Amyloid deposits are predominantly composed of amyloid fibrils which are very stable structures with a common cross core fold. Deposits are always rich in proteoglycans and glycosaminoglycans, some of which are tightly associated with the fibrils and further

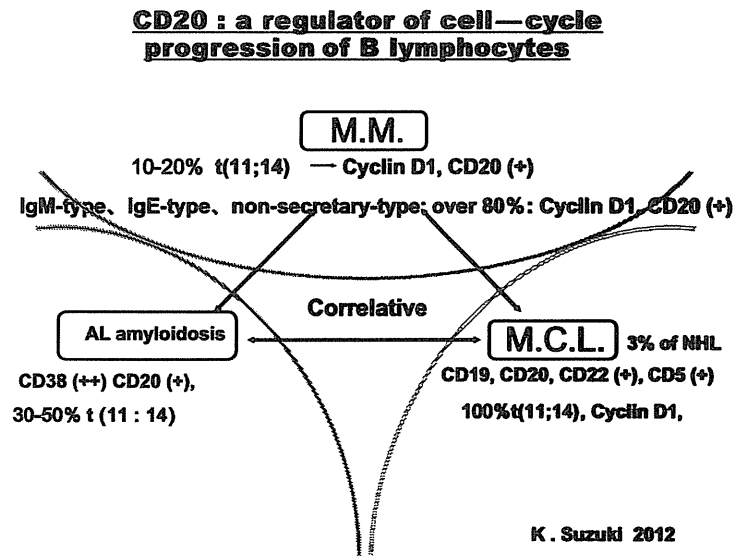


**Fig. 10** Correlation of pathogenesis between MM, AL amyloidosis and Mantle cell lymphoma by the up-regulated cyclin D1 function. Mantle cell lymphoma is high tumor growth with 100 % t (11:14), MM have 10–20 % t (11:14) with moderate growth and secretary Ig functions. Some strange and rear MM patients (i.e. IgM-type, IgE-type, non-secretary-type) showed translocation 11:14 over 80 %. Otherwise, AL amyloidosis showed 30–50 % t (11:14). There may be the differences of break points on the translocation foci

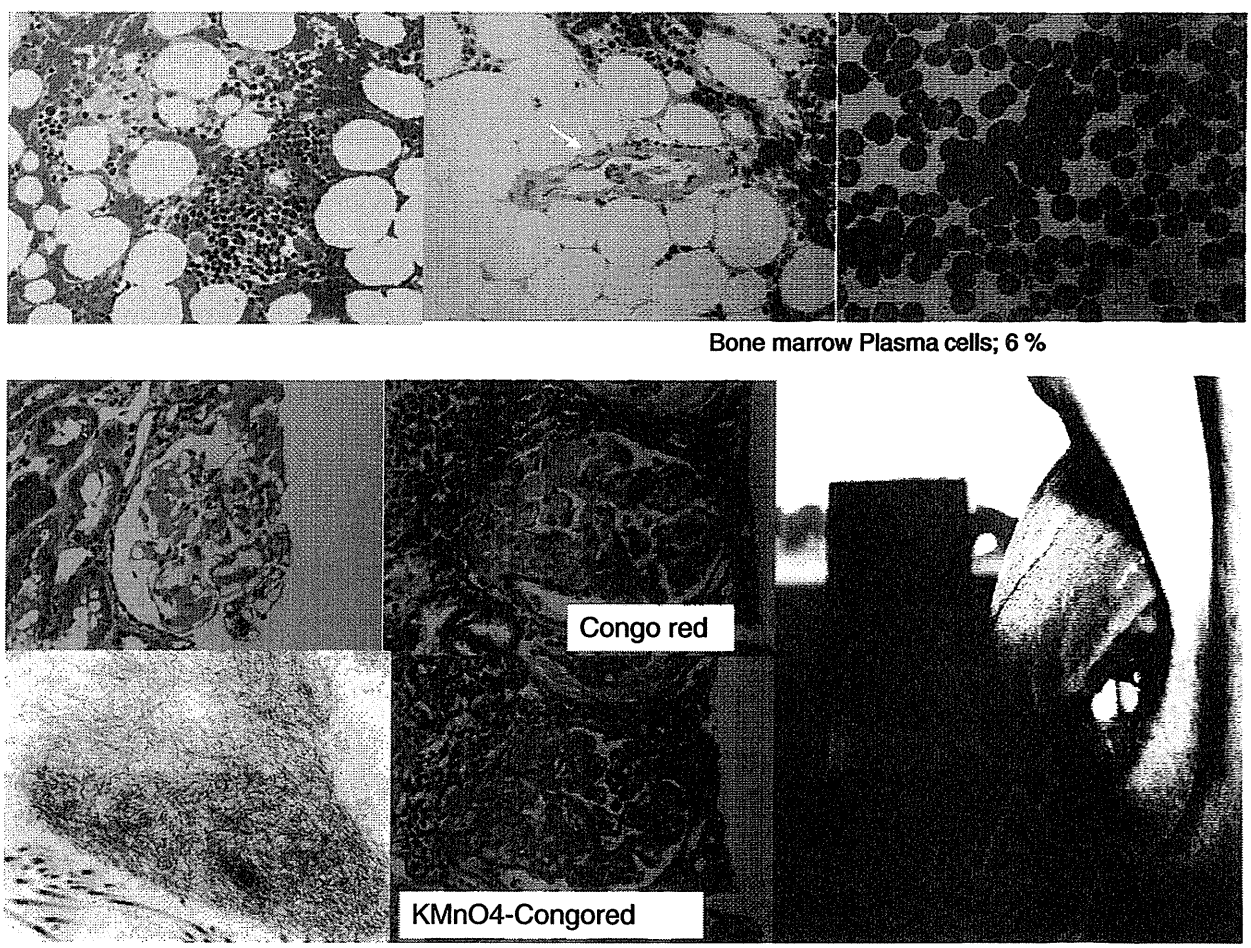


**Fig. 11** Histology of bone marrow and kidney. Tubercle in margin of tongue is important finding for diagnosis. The amyloidogenic plasma cell clone is mature type mainly CD19 negative clone. We can see amyloid deposition in blood vessels of bone marrow in some cases. Congo-red staining and amyloid fibrils by EM is important by the low detection with light chain staining

stabilize them against proteolytic degradation by phagocytes and affinities of selective organ deposition..

Renal dysfunction in AL amyloidosis is frequently caused by glomerular injury due to deposit of amyloid and observes high albuminuria and nephrotic syndrome. Its progression leads to kidney failure, and in many cases requires dialysis.

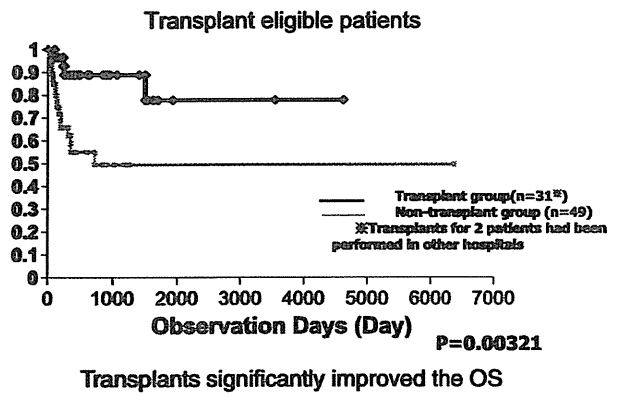


**Fig. 12** Autologous stem cell transplantation (ASCT) for AL amyloidosis. ASCT in the early stage of AL amyloidosis is effective for the OS and good QOL. In our experiences, group of ASCT showed good OS compared with the others ($P = 0.00321$)

## Therapy of AL amyloidosis

The target of chemotherapies is the amyloidogenic clonal plasma cells in the bone marrow. Complete remission is the normalized kappa/lambda ratio of serum FLC, the surrogate markers. Similar to MM, the recovery of function in the damaged organ requires the improvement of primary disease. However, the recovery from renal dysfunction with amyloid deposits requires a longer complete remission period. High-dose chemotherapy followed by autologous peripheral blood stem cells (ASCT) is effective in treating AL amyloidosis (Fig. 12).

The response criteria are roughly classified into hematological response comprised of elimination of M protein, etc. and organ response. In case of renal dysfunction, it is judged by decrease of albumin. The four-year survival rate in transplantation group and non-transplantation group is 71 and 41 %, respectively, showing higher survival rate in transplantation group [44], and in the patients who survive over 1 year and obtain complete remission after ASCT, over 10 years of prognosis can be expected [45]. In our faculty, we conducted high dose chemotherapy with ASCT during 2005–2010 in 15 patients with renal amyloidosis who were 65 years old or younger and had good PS, and every case showed good results (Fig. 13). Poor

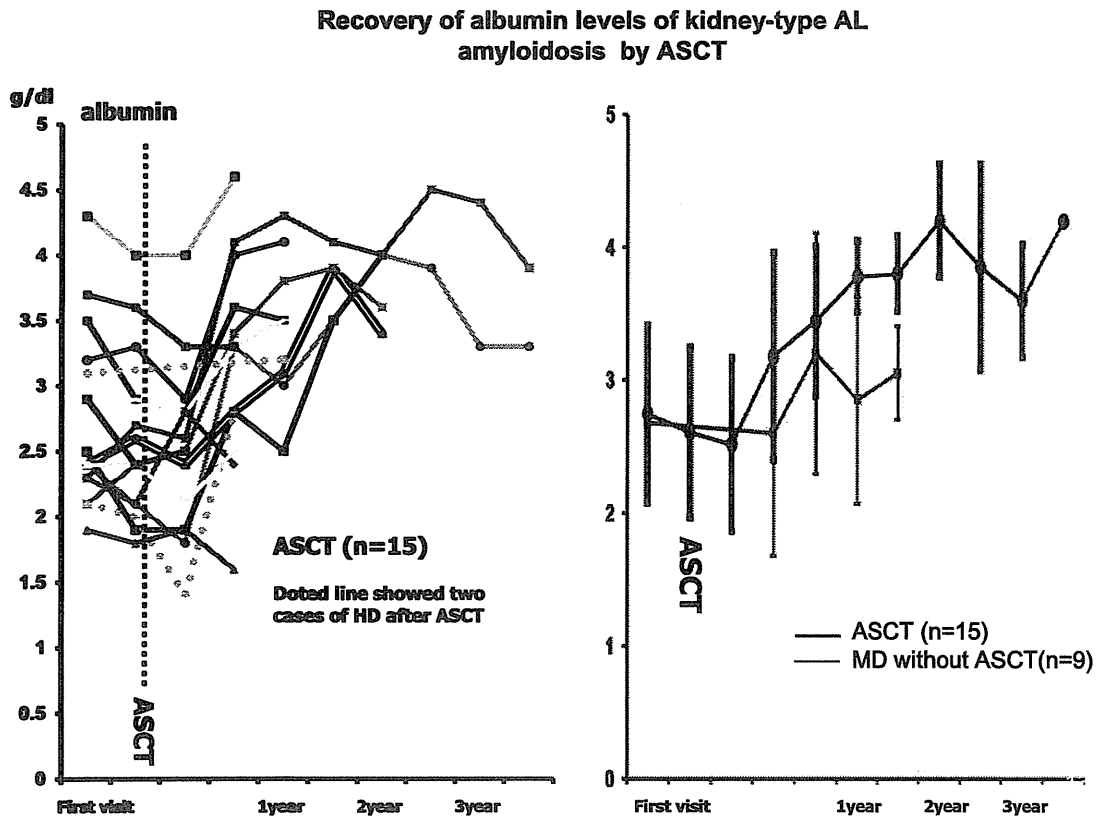


**Fig. 13** Effect of ASCT for renal type of AL amyloidosis. Early recoveries of the albumin concentration occurred by ASCT in the early stage

prognostic factors in high-dose chemotherapy are poor PS, symptomatic cardiac failure, organ failure in more than two organs (heart and kidney), and old age (over 65 years of age), and these cases are non-transplant candidates [46]. MD (melphalan and dexamethasone), thalidomide (Thal/Dex), cyclophosphamide-thalidomide (CTD), and the combinations of MM therapy are the first option for the transplant ineligible. In MD therapy, approximately 60–70 % of hematological improvement and approximately 50 % of improved organ were observed [47]. In overseas, clinical studies are conducted on novel agents (lenalidomide, thalidomide, and bortezomib) of myeloma in combination with melphalan, dexamethasone and cyclophosphamide against AL amyloidosis. Of these, bortezomib is considered most promising because improvement of organs can be expected in addition to its rapid hematological improvement with high rate. On the other hand, peripheral neuropathy and cardiotoxicity were reported as major adverse events of bortezomib, patients have to be carefully observed with these complications. Lenalidomide shows poor tolerability in AL amyloidosis patients at 25 mg/day which is a standard dose in multiple myeloma, and its MTD is 15 mg/day in AL amyloidosis. Around 50–70 % of hematological improvement and around 20–50 % of improvement in organs was reported in lenalidomide therapy of AL amyloidosis [48, 49]. Appropriate use of lenalidomide depending on the state of patients should be considered because it has a different profile of adverse events from bortezomib. Because thalidomide and lenalidomide were reported to worsen renal function in patients with renal amyloidosis, careful monitoring should be given when used in such patients. Transplantation of the involved organs is also an option in the overseas.

## Conclusion

As mentioned above, the therapy and treatment strategy of MM and AL amyloidosis have largely changed in these recent years. At same time, it is becoming more important to control the disease in a long-term fashion, maintaining QoL of patient because it is still difficult to cure the disease. The increase in the number of treatment options means that personalized medicine which selects a treatment corresponding to the systemic condition of the patient, and the purpose of the treatment will be more important. It is important to treat MM as chronic disease by taking into full consideration efficacy and safety of novel drugs and by effectively combining them with existing drugs. Also we should consider how we could help patients through the treatment to live long actively in the society.

MM and AL amyloidosis are caused by functional abnormality of monoclonal plasma cells, and high-dose chemotherapy supported with autologous peripheral blood stem cells is effective to these diseases. However, they are still difficult to be cured and require long-term disease control. In recent years, introduction of novel agents has changed their treatment strategies.

Better understanding of the biology of the amyloidogenic plasma cell clone and the molecular mechanisms underlying the light chain misfolding, tissue targeting and toxicity will define disease-related prognostic criteria. Risk-adapted therapeutic strategies may be required.

However, it is important to take these diseases as chronic diseases. For this purpose, early diagnosis and timing of initiation of treatments is important. Moreover, understanding of characteristics of novel agents and using them in combination with existing drugs appropriately for individual patient is critical. In addition, collaboration with renal medicine is essential to avoid introduction of dialysis. Also we should consider how we could help patients by treatment to live long actively in the society.



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# Current Therapeutic Strategy for Multiple Myeloma

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This is a review regarding the current therapeutic strategies in the management of multiple myeloma. Due to the introduction of several new effective therapeutic agents, multiple myeloma is one of the most active and changing fields in clinical oncology. Multiple myeloma is caused by the expansion of monoclonal plasma cells and secretion of M-protein (immunoglobulins, Bence Jones protein and free light chain). High-dose chemotherapy supported with autologous peripheral blood stem cells is an effective treatment for the disease. However, multiple myelomas are still difficult to cure and require long-term disease control. In recent years, the introduction of novel drugs (bortezomib, lenalidomide and thalidomide) has improved treatment.

*Key words: multiple myeloma – ASCT – SPM – renal insufficiency*

## INTRODUCTION

Multiple myeloma (MM) is an incurable disease with a high incidence rate in the elderly. Responsiveness to treatments varies largely among patients due to the high heterogeneity of MM. The decision of which treatment is best has been a difficult issue in MM. However, changes in treatment strategies can be seen due to the introduction of novel drugs (bortezomib, lenalidomide and thalidomide) that have been able to achieve good quality responses. The treatment of MM has advanced remarkably in recent years; this article reviews the latest trends and future outlook for the treatment of MM.

## HISTORY OF MYELOMA TREATMENTS

In 1962, Bergsagel et al. (1) reported that L-phenylalanine mustard (melphalan) could induce remission in approximately one-third of patients with MM. In 1967, Salmon et al. reported that high doses of glucocorticoids could induce remission in patients with refractory or relapsing MM (2). Combination therapy with melphalan and prednisolone in 1969 by Alexanian et al. had a better remission than melphalan alone (3). However, the response rate with alkylators and corticosteroids was only ~50%, and complete response (CR) was rare. A cure was never the goal of therapy, as it was assumed to be unattainable. Instead, the goal was to control the disease as much as possible, providing the best quality of life to patients for the longest duration by judicious, intermittent use of the two available classes of active chemotherapeutic agents. In 1986, clinical studies evaluating high-dose therapy with autologous stem-cell transplantation (HDT-ASCT) with single ASCT (McElwain) and double ASCT (Barlogie) were conducted. In 1996, the first randomized study showed the benefits of HDT-ASCT vs. standard chemotherapy. Berenson et al. described the efficacy of bisphosphonate pamidronate in reducing the skeletal events in patients with advanced MM. In 1999, both the thalidomide and the first non-myeloablative mini-allogeneic transplants were introduced with several novel agents that target the biological pathway of the disease, as well as long-acting Adriamycin® analogues. In the past decade, thalidomide, bortezomib and lenalidomide have emerged as effective agents for the treatment of myeloma, producing spectacular results in combination with other known agents in terms of response rate, CR rate, progression-free survival (PFS) and more recently, overall survival (OS) (Fig. 1).

In 2001, a new classification system introduced the CRAB (hyperCalcemia, Renal impairment, Anemia, Bone disease)

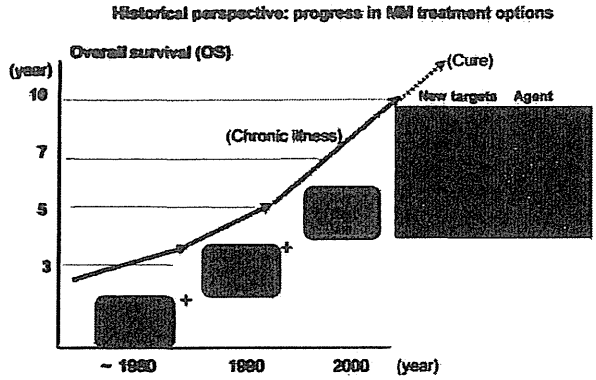


**Figure 1.** Historical perspective: progress in MM treatment options. 1970, MP; 1986, HDT with ASCT; 1999–2000, new drugs (bortezomib, lenalidomide and thalidomide) were epoch making. The CS-1 antibody (Elotuzumab) and IL-6 antibody (Siltuximab) may be effective with some combinations. Bendamustine, a bifunctional agent, shares properties of alkylating agents and purine analogs. New combination trials of new agents, as shown in the right side may be promising.

features of organ damage (4). In 2004, the International Staging System was introduced. The results obtained from new combinations have indeed been remarkable and have created a relatively new philosophy of treating myeloma with the goal of a potential cure rather than the disease control.

During the past two decades, HDT-ASCT has become the standard treatment option for patients with untreated MM who are <65 years of age; however, HDT-SCT is not usually recommended for older patients and patients with clinically significant co-morbidities.

A recent study has shown that long-term survival improved significantly in younger patients, while only limited improvement was achieved in elderly patients. Improved treatment for such older patients ineligible for HDT-SCT was much awaited. Should we treat patients with myeloma with multidrug, multitransplant combinations to pursue the goal of potentially curing a subset of patients, recognizing that the increase in adverse events (AEs) and decrease in the quality of life (QoL) will be substantial? Or, should we consider myeloma as a chronic incurable disease with a goal of disease control, using the least toxic regimens, emphasizing a balance between efficacy and the quality of life, and reserving more aggressive therapy for after relapse or the refractory phase.

## INDUCTION THERAPY FOR PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

The effect of novel agents on outcome in patients with newly diagnosed multiple myeloma (NDMM) was dramatically improved over previous therapies (5). Treatment of newly diagnosed MM and maintenance therapies are shown in the National Comprehensive Cancer network (NCCN) guidelines, version 1.2013.

### BORTEZOMIB

#### *BORTEZOMIB AND DEXAMETHASONE (DOUBLET)*

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. It is cytotoxic to a variety of cancer cell types *in vitro* and causes suppression of tumor growth *in vivo* in non-clinical tumor models, including MM. Specifically, bortezomib is effective in MM via its inhibition of nuclear factor-κB activation, its attenuation of interleukin-6-mediated cell growth (direct apoptotic effect), and possibly antiangiogenic and other effects (6). Bortezomib was approved in the USA in 2005 for the treatment of MM patients with a history of at least one prior therapy, based on the results from the Phase 3 Assessment of Proteasome inhibition for EXtending remission study, which showed superiority of bortezomib over high-dose dexamethasone in patients with relapsed MM (7). An Intergroupe Francophone du Myélome (IFM) Phase 2 study investigated BD as the induction therapy before transplantation in 48 patients with previously untreated MM (8). The response rate was 67%, including 21% CR or near complete remission (nCR) and 31% achieved at least a very good partial response (VGPR). Therefore, 55% of post-transplantation patients achieved VGPR or better. Toxicities were generally mild to moderate and proved manageable; there was no treatment-related mortality. In a report of 48 patients with untreated symptomatic myeloma, Jagannath et al. administered bortezomib 1.3 mg/m$^2$ twice weekly plus dexamethasone 40 mg on the day of and the day after bortezomib. The CR/nCR rate was 19%, and the partial response (PR) rate was 71%, giving a 90% overall response rate (ORR) (9).

#### *BD AND A CYTOTOXIC DRUG (DOXORUBICIN OR CYCLOPHOSPHAMIDE) (TRIPLET)*

In a Phase 3 study, the PAD regimen (bortezomib, dexamethasone and doxorubicin) was compared with VAD (vincristine, dexamethasone and doxorubicin) as induction therapy before ASCT (10). Superior CR/nCR rates were seen with PAD compared with VAD after both induction (11 vs. 5%, respectively) and ASCT (30 vs. 15%). PAD induction followed by ASCT and subsequent bortezomib maintenance was associated with significantly longer PFS and OS compared with VAD induction and post-ASCT thalidomide maintenance therapy. The (preliminary) overall CR rate including maintenance was 27% (PAD arm) and 5% (VAD arm), $P = 0.001$. Two additional Phase 2 studies confirmed the activity of a PAD-like induction regimen incorporating pegylated liposomal doxorubicin (11).

In addition, cyclophosphamide has also demonstrated substantial activity when combined with VD (CyBorD or VCD) in preparation for ASCT (12,13). In this trial, an additional 370 patients up to 60 years of age with untreated MM were enrolled to receive three 3-week cycles of induction treatment with V (1.3 mg/m$^2$ IV), Dex (40 mg/d oral) and

C (900 mg/m$^2$ IV) before scheduled high-dose melphalan and ASCT. All 370 patients (88.3% completed three cycles) were included in the intent-to-treat analysis. The ORR (ORR = CR + PR) was 84%, with 10% CR and 74% PR, 5.7% minor response (MR), 7.3% no change and 2.3% progressive disease.

### *Bortezomib, melphalan and prednisolone therapy*

Regarding the treatment of patients who are not eligible for transplantation, thalidomide, melphalan and prednisolone (MPT) and bortezomib, melphalan and prednisolone (MPB) have shown a significantly better OS benefit than that of MP and are the recommended treatments.

Five-year OS data from an MPB follow-up study have recently been published (14,15). After a follow-up period of 60.1 months, OS for those treated with MPB was significantly superior to those treated with MP; OS was 56.4 and 43.1 months, respectively. These data are remarkable because of the magnitude of improvement in OS (13.3 months). In comparison, MPT only showed an improvement in OS of 6.6 months in a meta-analysis (16). As a result of this VISTA study, MPB became the standard treatment for transplant-ineligible patients with NDMM.

To evaluate the safety, pharmacokinetics and efficacy of MPB therapy, we conducted a Phase 1/2 study for untreated Japanese MM patients who were ineligible for ASCT (17).

The continuity of treatment cycles and the incidence of interstitial lung disease were assessed. This Phase 1/2 study in Japan suggests that the recommended dose of bortezomib in MPB therapy is 1.3 mg/m$^2$ and that MPB therapy in newly diagnosed Japanese MM patients ineligible for ASCT is as effective as that shown in the VISTA trial.

In the past, achievement of a CR in MM was rare. New treatments can increase the rate of CR to the same level with high-dose therapy followed by ASCT (Fig. 2) (18–20). Also, the CR rate in Phase 3 trials in non-transplant patients

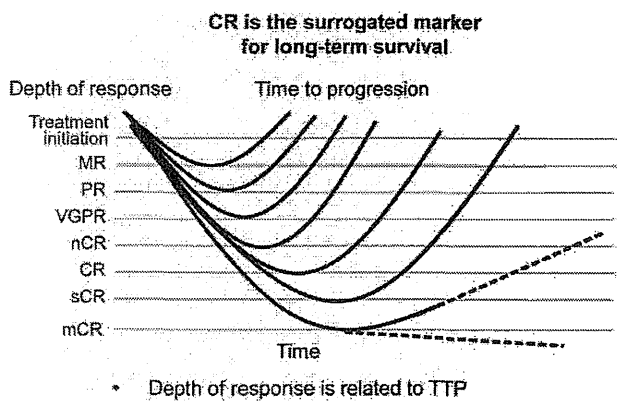


**Figure 2.** CR is the surrogated marker for the long survival. CR correlates with the long-term PFS and OS. Achieving CR and sustaining CR within a 3-year landmark from the treatment initiation was associated with highly superior survival. Adapted from refs Niesvizky et al. (18); Harousseau et al. (19); Chanan-Khan et al. (20).

was MPB, 30%; MPT, 16%; lenalidomide in combination with MP (MPR), 3.3% and lenalidomide in combination with MP followed by lenalidomide monotherapy (MPR-R), 9.9%.

### *Survival analysis of bortezomib administered subcutaneously vs. IV in patients with relapsed MM*

The Phase 3 MMY-3021 study compared the safety and efficacy of subcutaneously (SC) vs. IV administration of bortezomib in patients with relapsed myeloma (21). The Phase 1 study demonstrated non-inferior efficacy with SC vs. IV administration for the primary endpoint (ORR) after four cycles of single-agent bortezomib (22).

After a median follow-up of 11.8 months in the SC group and 12.0 months in the IV group, there were no significant differences in time to progression (median 10.4 vs. 9.4 months) or 1-year OS (72.6 vs. 76.7%) with SC vs. IV bortezomib, respectively. Peripheral neuropathy of any grade [56 (38%) vs. 39 (53%)]; $P = 0.044$], Grade 2 or worse [35 (24%) vs. 30 (41%); $P = 0.012$] and Grade 3 or worse [9(6%) vs. 12 (16%); $P = 0.026$] was significantly less common with SC than with IV administration. SC administration was locally well tolerated.

### Thalidomide and cyclophosphamide

The rationale for using thalidomide was based on its antiangiogenic properties because increased microvessel density in MM has been inversely correlated with survival. However, thalidomide has multiple modes of action, including immunomodulatory effects. This initial experience generated great enthusiasm and a large number of Phase 2 trials were conducted. A systematic review of 42 trials comprising >1600 patients confirm that the response rate is 29% with an estimated 1-year OS of 60%.

The well-known teratogenicity of thalidomide is not a major concern in patients with MM because of patient age, but still justifies careful informing of patients to avoid drug exposure in women with childbearing potential. The major toxicities of thalidomide are peripheral neuropathy, fatigue, somnolence and constipation, which are related to the daily dosage and treatment duration. The overall incidence of peripheral neuropathy is 30% but may be higher if treatment is prolonged for >1 year. Because this complication may be disabling and sometimes irreversible, patients should decrease the dose or stop treatment if significant numbness occurs.

### *Cyclophosphamide, thalidomide and dexamethasone therapy*

The MRC Myeloma IX trial was a large-scale, multi-center Phase 3 study conducted in the United Kingdom. This trial investigated the efficacy of treatment with cyclophosphamide, thalidomide and dexamethasone (CTD) as well as with its attenuated regimen (CTDa) for induction therapy, in comparison with the combination of cyclophosphamide, vincristine, doxorubicin and dexamethasone (CVAD) and MP

therapy. In transplant-eligible patients with NDMM, the CR rate after induction therapy was 13.0% in the CTD group vs. 8.1% in the CVAD group ($P = 0.0083$), and the CR rate after transplantation was 50.0 vs. 37.2%, respectively ($P = 0.00052$) (23). CTD therapy was superior to CVAD therapy at every time point, but PFS and OS did not differ significantly between the two groups (PFS, $P = 0.56$; OS, $P = 0.29$).

In transplant-ineligible patients, the ORR (≥PR) of the CTDa group was ~2-fold higher than the MP group (≥PR, 63.8 vs. 32.6%, $P < 0.0001$; CR, 13.1 vs. 2.4%, respectively). PFS was extended significantly with CTDa therapy compared with MP therapy (13.0 vs. 12.4 months, $P = 0.01$, respectively), whereas OS did not differ between these two groups (33.2 vs. 30.6 months, $P = 0.24$, respectively) (24). Therefore, a CTD regimen would be considered an efficacious oral regimen. Furthermore, dose adjustment for elderly patients would lead to an improvement in their treatment tolerability, as demonstrated in those given CTDa therapy.

#### *Bortezomib, thalidomide and dexamethasone therapy*

The MMY-3006 study led by the GIMEMA Italy compared bortezomib, thalidomide and dexamethasone (VTD) to TD as induction therapy followed by VTD vs. TD as consolidation therapy after tandem transplantations for transplant-eligible patients with NDMM. The CR rate after induction therapy was 22.5 vs. 5.6% (VTD vs. TD, $P < 0.0001$) and 48.7 vs. 40.4% ($P = 0.131$) after tandem transplantations, indicating the superiority of VTD therapy. Furthermore, the estimated 3-year-PFS rate was 60% in the VTD group vs. 48% in TD group ($P = 0.043$)(25). AEs (Grade 3/4) that occurred at a higher frequency in the VTD group (compared with TD) during the induction therapy were skin rash ($P = 0.0001$) and peripheral neuropathy ($P = 0.0004$). Incidence rates of constipation ($P = 0.45$), deep-vein thrombosis ($P = 0.53$) and infection excluding herpes zoster ($P = 0.35$) were comparable between the two groups (26).

The above findings suggest promising potential of VTD therapy for induction therapy prior to transplantation based on its greater CR rate and a longer PFS compared with TD therapy. However, reduced-dose VTD (V, 1.3 → 1.0 mg/m$^2$; T, 200 → 100 mg/day) is an imperative point in order to prevent the appearance of peripheral neuropathy upon administration of both bortezomib and thalidomide with slightly reduced efficacy (27).

### Lenalidomide

Lenalidomide is one of the immunomodulatory derivatives of thalidomide and has more potent biologic activities, such as direct anti-myeloma effects, via the production of IL-2 and IFN-γ, which lead to the activation of cytotoxic T cells and natural killer (NK) cells and inhibition of IL-6 and TNF-α production for the survival of MM cells (28). Recently, cereblon, which is composed of E3 ubiquitin ligase complex, has been identified as the target molecule of lenalidomide and required for both direct anti-myeloma activities and the induction/inhibition of cytokines/growth factors from T cells and bone marrow stromal cells. Lenalidomide especially down-regulates the expression of IRF-4, which is critical for the survival of MM cells and the knock-down of cereblon leads to the down-regulation of IRF-4 and apoptosis in MM cells (29,30). As seen in *in vitro* growth inhibition and apoptosis of MM cells by lenalidomide, the administration of lenalidomide is effective in patients with high IRF-4 expression who have a poor prognosis in comparison with those with low IRF-4 expression (31).

Two randomized Phase 3 trails (MM-009/010) compared lenalidomide plus high-dose dexamethasone and high-dose dexamethasone monotherapy in patients with relapsed/refractory multiple myeloma (RRMM). Lenalidomide showed better efficacy for response rate, time to progression (TTP) and OS (32,33). A pooled analysis of these two studies showed that ORR and CR rates were improved for patients who received lenalidomide over those who did not (ORR: 60.6 vs. 21.9%, $P < 0.001$; CR: 15 vs. 2.0%, $P < 0.001$, respectively). A significant increase in OS was also seen in the lenalidomide treatment group after a median of 48 months of follow-up (median 38.0 vs. 31.6 months), despite the cross-over of 47.6% of the placebo group to the lenalidomide treatment group after disease progression (34). The most frequent AEs were neutropenia, thrombocytopenia and thromboembolic events.

Lenalidomide plus high-dose dexamethasone (RD: lenalidomide 25 mg d.1–21, dexamethasone 40 mg d.1–4, 9–12, 17–20, every 4 weeks) is highly efficacious in RRMM patients, but is associated with a high incidence of thromboembolic complications and severe AEs (SAEs). Therefore, an adopted regimen of lenalidomide plus low-dose dexamethasone (Rd: lenalidomide 25 mg d.1–21, dexamethasone 40 mg d.1, 8, 15, 22, every 4 weeks) was evaluated for efficacy and safety compared with RD in NDMM (35). The ORR of Rd was lower (70%) than that of RD (81%), but PFS and the 1-year OS of Rd was longer (PFS, 25.3 months; OS, 96%) than that of RD (PFS, 19.1 months; OS, 87%). These results seemed to be associated with treatment-related toxicities. The Rd regimen is an effective treatment with acceptable toxicity and the early mortality of Rd was lower (0.5%) than that of RD (5%).

### Zoledronic acid (Zometa) and denosumab: prevention of skeletal-related events

Interactions between myeloma cells and bone marrow stromal cells are fundamental to the excessive activation and proliferation of osteoclasts causing localized bone destruction (36). Myeloma cells also secrete factors that inhibit osteoblasts, blocking the repair of osteolytic damage. The resulting bone lesions place patients at risk of skeletal-related events such as pathological fractures, the need for surgery or

palliative radiation to the bone and spinal cord compression. Bisphosphonates (BPs) and denosumab were developed mainly to impair malignant osteolysis, thereby breaking the cycle of bone destruction and cancer growth that can result in skeletal-related events. By blocking the growth-factor release from the bone matrix, BPs can indirectly impede myeloma growth. BPs, such as zoledronic acid (Zometa), inhibit osteoclast-mediated osteolysis and are the pharmacological standard of care for patients with myeloma bone disease (37). BP or denosumab therapy for MM is generally well tolerated (38). Potential AEs from BP therapy for MM include inflammatory reactions at the injection site, acute phase reactions following IV use, hyperthermia and hypocalcemia. Additionally, renal impairment and osteonecrosis of the jaw are infrequent but serious complications that can result from BP therapy.

## MAINTENANCE THERAPY FOR MULTIPLE MYELOMA

Post-transplant consolidation/maintenance with novel agents can become an important step forward. Thus, it has recently been reported that post-transplant consolidation with thalidomide, lenalidomide or bortezomib increases the CR rate.

After induction treatment, two to four cycles of consolidation therapy are followed by maintenance, which is continuous therapy with a single agent with reasonable balance between maximum benefits and minimum toxicities until the time of disease progression (39).

Introduction of ASCT and novel agents into therapeutic regimens for MM have improved patients' response rates and survival rates markedly. However, the majority still experience disease recurrences, which have led to particular importance being placed on maintenance therapy. In this setting, several clinical studies are underway to evaluate maintenance therapies using mainly thalidomide, lenalidomide or bortezomib. Among those, the studies investigating thalidomide for its efficacy as maintenance therapy are foremost.

Attal et al. of IFM conducted the IFM 99-02 study. All subjects received tandem ASCT therapy followed by one of the three maintenance arms: no maintenance; pamidronate or pamidronate plus thalidomide. The first two arms were found to be inferior to the last arm in the response rate (≥VGPR) (55 vs. 57 vs. 67%, respectively). Furthermore, an additional analysis combining first two group (no-thalidomide) against the thalidomide-maintenance group revealed a significant improvement in event-free survival (EFS) and OS for the thalidomide group (EFS, $P = 0.003$; OS, $P = 0.04$) (40). Moreover, Spencer et al. of Australia conducted the ALLG MM6 study to investigate the consolidation therapy post-single ASCT by comparing a thalidomide plus prednisolone group with a prednisolone-alone group. This study also demonstrated superior efficacy of the combined therapy with thalidomide based on its elevated response rate and significantly prolonged PFS and OS (PFS, $P < 0.001$; OS, $P = 0.004$) (41).

To evaluate the efficacy of bortezomib solely for maintenance therapy, a study involving this agent only in the maintenance therapy needs to be conducted, since the previous studies with bortezomib include it in both induction therapy as well as maintenance therapy.

I prefer disease control as a treatment goal, except in selected high-risk patients in whom an aggressive approach to achieving CR may be the only option for long-term survival. The disease control approach involves targeting VGPR (minimal residual disease) rather than CR by using limited, less intense therapy first and moving to more aggressive approaches as the need arises (sequential approach). This allows patients to help determine the timing and number of transplants.

We performed a prospective pilot study of sequentially registered subjects to determine the significance of BD maintenance therapy for long-term survival with good QoL. From September 2008, we continued an exploratory study of the effects of bortezomib on the ability of patients with relapsed, refractory, MM to continue maintenance therapy (42). Long-term survival with good QoL is the most important goal for elderly/low genetic risk MM patients. BD maintenance is a good and available option for this group (24/43 cases) over 20 months, especially in the cases where the total delivery dose is >40 mg.

Lenalidomide is an attractive agent for maintenance after induction therapy. The use of lenalidomide in combination with dexamethasone enhances its anti-myeloma activities, but inhibits the immunomodulatory effects of lenalidomide (43). Therefore, single-agent use of lenalidomide seems to be a logical option to enhance cytotoxic $CD8^+$ T-cell and NK-cells activity for immune surveillance. The effects of continuous lenalidomide monotherapy in ASCT-eligible and -ineligible patients have been investigated in three randomized Phase 3 studies (44,45). In ASCT-ineligible elderly patients, MPR-R resulted in better PFS compared with the MP or MPR regimens (MPR-R vs. MPR vs. MP: 31 months, 14 months ($P < 0.001$) and 13 months ($P < 0.001$), respectively. (46) In a landmark analysis, lenalidomide maintenance significantly prolonged PFS from the start of lenalidomide monotherapy compared with the MPR regimen (median PFS: 26 vs. 7 months). However, there were no differences in OS among these three regimens.

Two trials investigating lenalidomide maintenance for ASCT-eligible patients (CALGB100104 and IFM 2005-02 trials) were performed with or without consolidation (44,45). The consolidation with lenalidomide in IFM 2005-02 resulted in an increased CR rate from 14 to 20% ($P < 0.001$). The three-year PFS in the maintenance arm was 66% in CALGB100104 and 59% in IFM 2005-02 compared with those in the placebo arm, which were 39 and 35%, respectively, indicating that lenalidomide maintenance significantly improved PFS. On the other hand, the CALGB100104 trial showed significant improvement in OS (85 vs. 77% of patients were alive at the time of analysis, $P = 0.03$) despite crossover from the placebo arm to the lenalidomide

maintenance arm. However, second primary malignancy (SPM) is a serious event and the risk of SPM must be identified (47). The impressive benefits of lenalidomide maintenance must be weighed against the incidence of SPMs (48).

## TANDEM AUTOLOGOUS TRANSPLANTATION AND AUTOLOGOUS PLUS REDUCED-INTENSITY CONDITIONING ALLOGENEIC TRANSPLANTATION

High-dose melphalan with autologous stem cell support has been an integral part of MM therapy for more than 20 years, either as salvage therapy or as consolidation of an initial remission. Tandem autologous transplantation (TA) and autologous plus reduced-intensity conditioning allogeneic transplantation (AR) in the management of NDMM has a defined role in the upfront treatment of MM, but nearly all patients may relapse. AR is associated with a higher chance of achieving CR but also with a 3-fold increase in transplant-related mortality (TRM) when compared with TA in the upfront management of MM (49). However, there was a long-term survival among the 40–50% of patients who achieved molecular remission. Substantial innovative measures are necessary to either reduce the TRM and/or enhance the graft-vs.-myeloma effect before allogeneic transplantation can be reassessed in the upfront management of MM.

## THERAPY FOR RRMM

There are few effective salvage regimens available for patients with disease resistant to novel agents. The salvage therapy of MM is shown in the NCCN guidelines 1.2013.

**Table 1.** SPMs: incidence of MDS/AML from the diagnosis of myeloma

| | 95% confidence interval | | |
|---|---|---|---|
| | Estimate (%) | Lower (%) | Upper (%) |
| **The cumulative incidence of second MDS/AML (95% CI) at 12 years from the time of diagnosis of MM** | | | |
| 1 year | 1 | 0 | 5 |
| 8 years | 3 | 1 | 9 |
| 12 years | 7 | 2 | 19 |
| **The cumulative incidence of second MDS/AML (95% CI) after commencing len-based regimens** | | | |
| 1 year | 1 | 0 | 5 |
| 2 years | 4 | 1 | 9 |
| 3 years | 9 | 4 | 12 |

1-, 8- and 12-year cumulative MDS/AML incidence by the conventional drugs were the same with the incidence of MDS/AML from the initiation of lenalidomide 1-, 2- and 3-year cumulative incidence.
Adapted from Reece et al. *Blood* (ASH Annual Meeting Abstracts) 2010;116 (Abstract 1877).

### BORTEZOMIB RETREATMENT IN RELAPSED MULTIPLE MYELOMA

Retreatment with bortezomib appears to be a feasible treatment approach in patients with relapsed MM. A retrospective survey of patients with MM in 36 centers in Germany and Switzerland showed an ORR of 63% when retreating patients with bortezomib monotherapy or a combination of bortezomib with dexamethasone. At retreatment, 27 patients (64.3%) received concomitant dexamethasone and 47.6% of patients received other concomitant medications during bortezomib retreatment, including 14.3% who received concomitant anti-neoplastic or immunomodulating agents. Out of the 28 patients who had PR on initial treatment, 2 responded with nCR and 13 responded with PR on retreatment (50). The response rate was examined according to first treatment-free interval (TFI) ($\leq$6 vs. >6 months) and use of concomitant dexamethasone with bortezomib retreatment (yes vs. no). The response rate to bortezomib retreatment in the subgroup with first TFI >6 months was higher than that in the subgroup with first TFI $\leq$6 months (74.1 vs. 46.7%). The median time to response with bortezomib retreatment was 2.8 months. The median second TFI after bortezomib retreatment was 5.7 months. The median TTP after bortezomib retreatment was 10.5 months.

## ANALYSIS OF SPM

Another important issue in MM is the risk of developing SPMs due to patients living longer after diagnosis. Long follow-up analyses of MM-009/010 in RRMM shows that the long-term use of lenalidomide did not increase the incidence of SPM compared with all patients and the incidence of SPM with the long-term use of lenalidomide was within the expected range (median treatment duration, 46.2 vs. 9.8 months; incidence of myelodysplastic syndrome (MDS), 0 vs. 0.4; solid tumor, 1.8 vs. 1.3; non-melanoma skin cancer, 2.3 vs. 2.4) (51). It was concluded that the benefits continue to outweigh the risks and that as a consequence the benefit/risk balance of lenalidomide is positive under normal conditions of use. Population studies show that MM patients have an increased risk of acute myeloid leukemia (AML). Some MM therapeutic agents are particularly associated with an elevated risk of SPMs and melphalan is associated with an increased risk of secondary acute leukemia.

By summarizing the data to date, the incidence of all/invasive SPM is significantly increased in lenalidomide treatment arms, driven by hematologic SPM ($P < 0.001$). The overall benefit–risk profile of lenalidomide in NDMM remains positive (Table 1) (52). Risk factors for SPMs with lenalidomide by univariate and multivariate analyses in IFM 2005 may be treatment duration >24 months, male, age >55 years, International Staging System (ISS) stage III and previous exposure to alkylators.

In a report on a retrospective analysis of 325 Japanese MM patients from 1998 to 2010 (13 years), we showed that *t*-MDS/AML developed in 17 (5.2%) patients. The median

time to onset was 60 months in *t*-AML and 88 months in *t*-MDS. All patients with *t*-AML died within 8 months, and were suspected to be treated with melphalan; none had been given lenalidomide (53). There appears to be an increased risk for secondary cancers, especially with melphalan administration and lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

## RENAL DYSFUNCTION IN MULTIPLE MYELOMA

The timing of treatment initiation in MM is dependent on the existence of organ dysfunction. When bone symptoms, renal dysfunction, anemia or hypercalcemia is observed, symptomatic MM is diagnosed and treatment should be started. Renal dysfunction in MM is one of the complications that require the most careful attention and occurs via various mechanisms. Of these, the most frequent is cast nephropathy, also known as myeloma kidney, in which excessive light chains of M protein [Bence Jones protein (BJP)] secreted by proliferated plasma cells form casts and deposit themselves in renal tubules. In addition, hypercalcemia associated with osteolysis by myeloma cells, deposition of amyloid in glomeruli, hyperviscosity syndrome, hyperphosphatemia and renal infiltration of myeloma cells are also causes of renal dysfunction. Care must also be given to recurring urinary tract infection, drugs and dehydration that may act as exacerbating factors. According to the Japanese Society of Myeloma, ~15% of NDMM patients have a renal dysfunction complication and the rate increases as the disease progresses. BJP and immunoglobulin D (IgD) types of myeloma excrete high amounts of BJP into the urine and show a high frequency of renal dysfunction.

It has been reported that renal dysfunction remains reversible when serum creatinine is <4 mg/dL, Ca <11.5 mg/dL and urine protein ≤1 g/day (54). Although these are the data before the introduction of novel agents, in the 423 patients with NDMM, patients with renal dysfunction (22%) showed significantly shorter survival time compared with patients with normal renal function (8.6 vs. 34.5 months).

**Table 2.** Complete response (CR) renal

| Renal response | CC based ($n = 32$) | IMiDs based ($n = 47$) | Bortezomib based ($n = 17$) |
|---|---|---|---|
| CR renal (%) | 41 | 45 | 71 |
| | 47 | 45 | 82 |
| ≧MR renal (%) | 59 | 79 | 94 |
| Time to response (months) | 1.8 | 1.6 | 0.69 |
| Stages | | GFR (ml/min/1.73 $m^2$) | |
| 1 | Kidney damage with normal or elevated GFR | Over 90 | |
| 2 | Kidney damage with mild reduction of GFR | 60–89 | |
| 3 | Moderate reduction of GFR | 30–59 | |
| 4 | Severe reduction of GFR | 15–29 | |
| 5 | Renal failure | Below or hemodialysis | |
| Response | Baseline eGFR (ml/min/1.73 $m^2$) | Best CrCl response (ml/min)[a] | |
| CR renal | <50 | ≥60 | |
| PR renal | <15 | 30–59 | |
| MR renal | <15 | 15–29 | |
| | 15–29 | 30–59 | |

CR may be attained by a bortezomib-based regimen not only the high levels percentage but also time to response. Five stage is divided as the figure. The table is adapted from M. Roussou et al. *Leukemia Res* 34, 1395–1397, 2010.
[a]Must be maintained for ≥2 months.

### IMPROVEMENT OF RENAL FUNCTION AND TREATMENT STRATEGY FOR MULTIPLE MYELOMA

An improvement in patient's MM is the best remedy for their complicating renal dysfunction. Since 2005, the treatment strategy for MM has significantly changed due to the successful introduction of novel agents. The three drugs, including a proteasome inhibitor (bortezomib) and two immunomodulatory drugs (IMiDs) (lenalidomide and thalidomide), are referred to as novel agents, and each drug has characteristic efficacy and safety profiles. While all of these agents can be expected to restore renal function due to the improvement in the primary disease, bortezomib, with a strong antitumor effect, is reported to rapidly improve renal function (Table 2). The renal response rate is (minor response and better) based on improving creatinine clearance and time to response. The creatinine clearance improvements and times to response were 59% and 1.8 months (chemotherapy); 79% and 1.6 months in (IMiDs) and 94% and 0.69 month (bortezomib) (55).

## PERSONALIZED THERAPY IN MM ACCORDING TO PATIENT AGE AND VULNERABILITY

Most patients with NDMM are >65 years old with 30% >75 years. Elderly patients are more susceptible to side effects and are often unable to tolerate full drug doses (56). For these patients, lower dose-intensity regimens improve the safety profile and thus optimize treatment outcome. The

occurrence of serious hematological and non-hematological AEs during treatment should be carefully taken into account to adjust doses and optimize outcome.

## CONCLUSION

As mentioned above, the therapy and treatment strategy of MM have largely changed in recent years. Ongoing efforts to improve the treatment paradigm even further include using oncogenomics to better characterize molecular pathogenesis and to develop refined patient stratification and personalized treatment in MM using immune-based therapies including monoclonal antibodies, cytokines and novel immunocytic (NK, DC and γδT cells) strategies (57). At the same time, it is becoming more important to control the disease in a long-term fashion, maintaining the QoL of the patient because it is still difficult to cure this disease. The increased number of treatment options means that personalized medicine which selects a treatment corresponding to the systemic condition of the patient, and the purpose of the treatment will be more important. For this purpose, early diagnosis and timing of initiation of treatments are important. Moreover, understanding the characteristics of novel agents and using them in combination with existing drugs appropriately for the individual patient is critical. In addition, collaboration with renal medicine is essential to avoid the introduction of dialysis. And finally, we should be considering how we can help patients through the treatment to live long, active lives.

## Conflict of interest statement

None declared.

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