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Review Article

Strategy for Maintenance Therapy for Transplant-eligible and Non-eligible Patients with Multiple Myeloma

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Summary

Multiple myeloma (MM) is a hematological malignancy originating from plasma cells producing immunoglobulin. Introducing high-dose melphalan therapy followed by auto stem cell transplantation (ASCT) and novel drugs has improved the survival of patients with MM. The importance of maintenance therapy after induction therapy has been investigated to obtain a long duration of progression-free survival (PFS) after induction therapy. The role of maintenance therapy in MM is to inhibit disease progression after induction therapy without physical and financial burden for patients. Physical burden mainly refers to the side effects of treatment. Preventing relapse with minimum burden is beneficial. Here, we review the updated progress of maintenance therapy for transplant-eligible and -ineligible patients with MM. The results of clinical studies about maintenance therapies using thalidomide, lenalidomide, bortezomib, and ixazomib are demonstrated. The possible choice of treatment based on these results is suggested, and the utility of drug combination as a maintenance therapy is discussed. Furthermore, we describe the outline of the clinical trial we just commenced. We started an ixazomib maintenance therapy for transplant-ineligible patients intolerant to lenalidomide (IMTIL) study (UMIN000048285) to determine the efficacy and safety of ixazomib maintenance therapy in transplant-ineligible patients with MM who cannot be treated with standard doses of lenalidomide due to adverse reactions or frailty during or after induction therapy. In addition, the relationship between the efficacy of ixazomib in maintenance therapy and driver mutation and immune status is assessed.

Key Words: multiple myeloma, maintenance therapy, lenalidomide, bortezomib, ixazomib

Introduction

Multiple myeloma (MM) is a plasma cell-derived malignancy, and treating MM is challenging. The introduction of auto stem cell transplantation (ASCT) and other novel therapeutic agents, including a proteasome inhibitor (bortezomib), immunomodulatory drugs (IMiDs, including thalidomide, lenalidomide, and pomalidomide), and therapeutic antibodies, has improved the survival rates of patients with MM. ASCT with high-dose melphalan therapy in younger patients without major cardiac and pulmonary problems is expected to reduce many tumor burdens. For transplant-ineligible patients, combination therapies using a thera-

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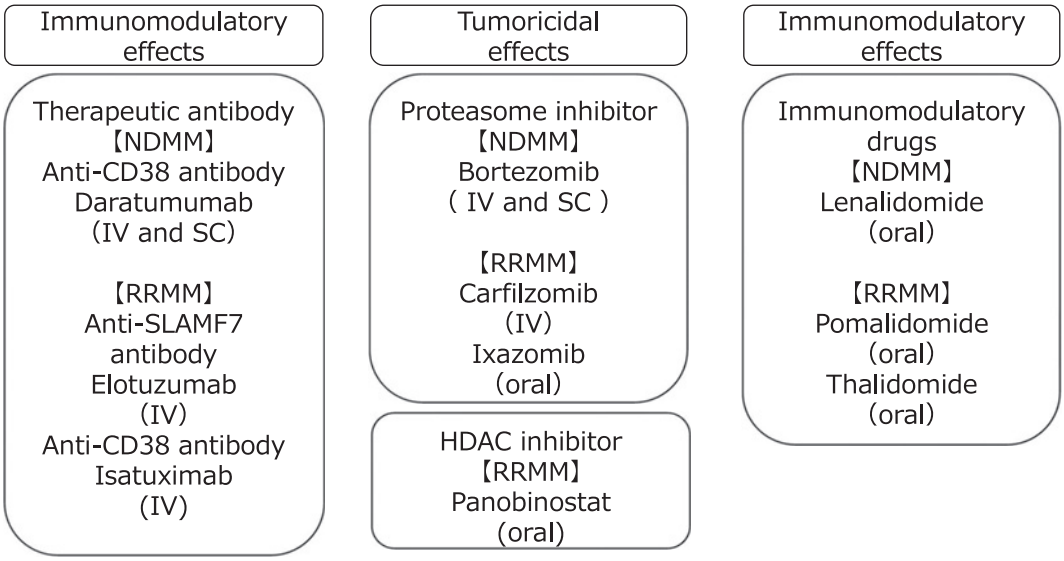

Figure 1 Illustration of available drugs for patients with multiple myeloma in Japan.
NDMM, newly diagnosed multiple myeloma; IV, intravenous injection; SC, subcutaneous injection; RRMM, relapsed/refractory multiple myeloma.

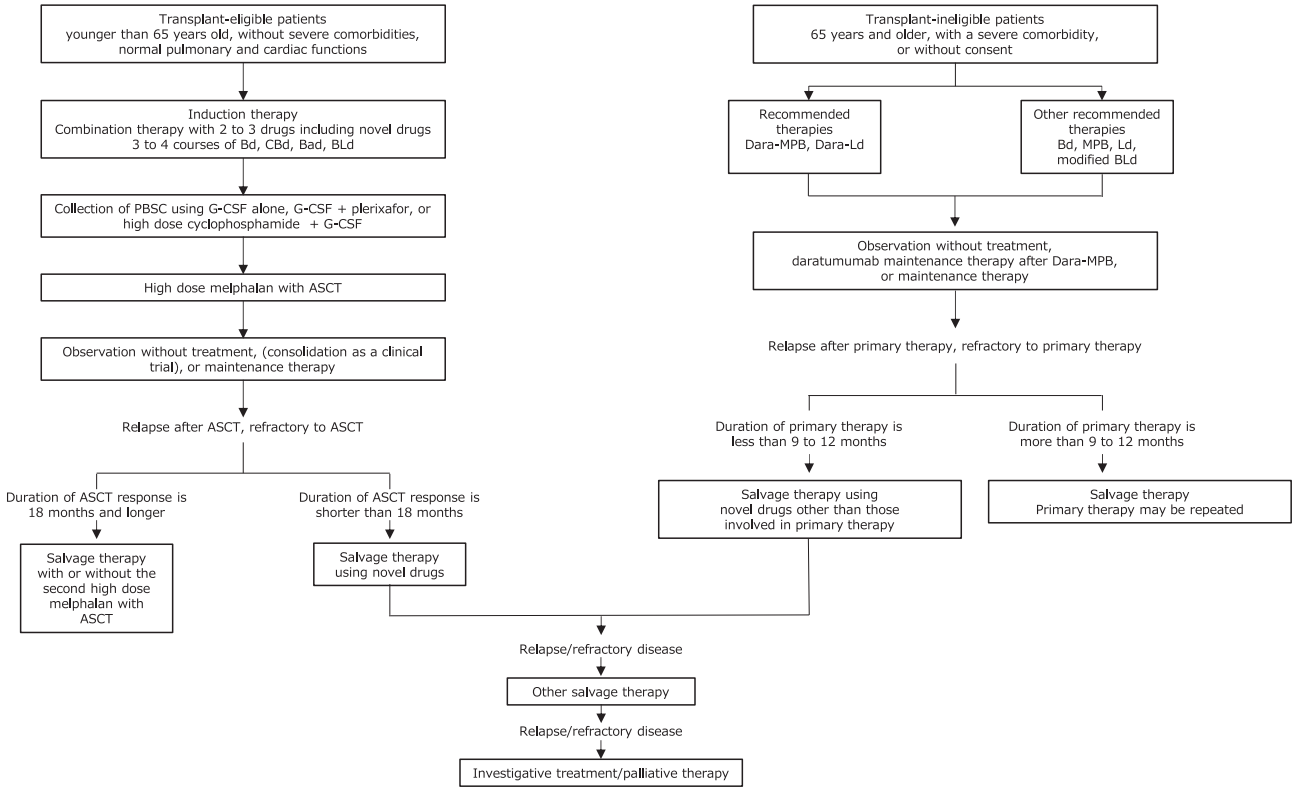

Figure 2 Treatment strategy for transplant-eligible and transplant-ineligible patients with MM.
Bd, bortezomib and dexamethasone; CBd, cyclophosphamide, bortezomib, and dexamethasone; Bad, bortezomib, doxorubicin, dexamethasone; BLd, bortezomib, lenalidomide, dexamethasone; PBSC, peripheral blood stem cell; G-CSF, granulocyte colony-stimulating factor; ASCT, auto stem cell transplantation; Dara-MPB, daratumumab, melphalan, prednisolone, bortezomib; Dara-Ld, daratumumab, lenalidomide, dexamethasone; Ld, lenalidomide, dexamethasone.

peutic antibody with a proteasome inhibitor or IMiD produce a greater response. Fig. 1 and 2 illustrate the available drugs and treatment strategies, including maintenance therapy, for patients with MM in Japan, respectively[1]. However, many relapsed/refractory MM patients remain; therefore, new therapies are expected to prevent relapse and refractoriness. Improvement of induction therapies has resulted in improved response[2]. The sustained reduction of tumor burden after induction therapy by maintenance therapy will increase the duration of progression-free survival (PFS). The role of maintenance therapy in MM is to reduce the disease progression after induction therapy without physical and financial burden on patients. Physical burden refers to the side effects of treatment. Preventing relapse with minimum burden is beneficial. Maintenance therapies using IMiDs, such as thalidomide and lenalidomide, as well as bortezomib, a proteasome inhibitor administrated intravenously or subcutaneously, have been estimated in several clinical studies. In addition, maintenance therapy with ixazomib, an orally available proteasome inhibitor, is available as an insurance-approved therapy in Japan. Herein, we update the clinical insights in maintenance therapy for patients with MM.

Thalidomide

Thalidomide is the first IMiD approved for patients with MM, and six randomized controlled trials (RCTs) (IFM99-02, ALLG MM6, TT2, HOVON50, MRC Myeloma IV, and NCIC CTG MY.10) compared the efficacy of thalidomide maintenance therapy and control after ASCT[3,4]. Thalidomide maintenance therapy promoted improvement of response rate and elongation of PFS; however, a significant improvement in overall survival (OS) was only observed in IFM99-02 and ALLG MM6. Side effects of thalidomide, such as peripheral neuropathy (PN) and deep vein thrombosis (DVT), were observed[5]. Furthermore, the Myeloma IX study included thalidomide maintenance therapy after CTD (cyclophosphamide, thalidomide, dexamethasone) or CVAD (cyclophosphamide, bortezomib, doxoribicin, dexamethasone) induction therapy and revealed that the duration of OS in patients treated with thalidomide maintenance therapy was shorter than that in patients without maintenance therapy in adverse cytogenetic abnormalities such as gain(1q), del(1p32), t(4;14), t(14;16), t(14;20), or del(17p)[6]. Thus, introducing thalidomide maintenance therapy after ASCT for patients with adverse cytogenetic abnormalities is not recommended.

Four clinical trials have examined the usefulness of thalidomide maintenance therapy for transplant-ineligible patients. In GIMEMA and HOVON 49 trials, melphalan, prednisolone, and thalidomide (MPT) and thalidomide maintenance therapy was compared with MP without maintenance therapy[7,8]. In these studies, addition of thalidomide to MP improved response rate and PFS, however, the superiority of MPT to MP in OS was not confirmed.

Bortezomib, melphalan, prednisolone, and thalidomide with bortezomib and thalidomide maintenance (VMPT-VT) or VMP was randomly assigned to transplant-ineligible patients. The median PFS was significantly improved by VMPT-VT (35.3 months) as compared with VMP (24.8 months) (Hazard ratio (HR), 0.58; 95% CI, 0.47 to 0.71, $P < 0.001$). The 5-year OS was higher with VMPT-VT (61%) than with VMP (51%; HR, 0.70; 95% CI, 0.52 to 0.92, $P = 0.01$). Grade 3 to 4 neutropenia, PN, cardiologic and thromboembolic events were more frequent in the VMPT-VT group than the VMP group[9].

In the HOVON87/NMSG18 study, thalidomide maintenance therapy after MPT (MPT-T) was compared with lenalidomide maintenance therapy after MPR (melphalan, prednisolone, and lenalidomide) (MPR-R)[10]. The PFS and OS in MPT-T were not superior to those in MPR-R, and PN was more common in MPT-T than in MPR-R.

Lenalidomide

The comparison of lenalidomide maintenance therapy with placebo after ASCT was performed in three prospective randomized clinical trials, including IFM 2005-02, CALGB100104, and GIMEMA RV-MM-PI-209, and a meta-analysis of these trials[11-14]. In the IFM2005-02 trial, patients were randomly assigned to lenalidomide maintenance or placebo groups after single or tandem ASCT and Ld (lenalidomide and dexamethasone) consolidation[11]. In the CALGB100104 trial, patients were randomly assigned to lenalidomide maintenance or placebo groups until disease progression (PD) after a single ASCT[12]. In the GIMEMA RV-MM-PI-209

trial, 273 patients ≤ 65 years old were randomly assigned to high-dose melphalan plus ASCT or MPR consolidation therapy after induction, and 251 patients were assigned to lenalidomide maintenance therapy or no maintenance therapy[13]. Prolongation of PFS by lenalidomide maintenance therapy compared with placebo or observation after ASCT was demonstrated in all three trials. Although PFS was the primary endpoint in all studies, OS was not a primary endpoint. Thus, a meta-analysis was conducted to better understand the impact of lenalidomide maintenance after ASCT[14]. In the meta-analysis, 605 patients of the lenalidomide maintenance group and 603 of the placebo or observation group were included. The median PFS was superior in the lenalidomide group (52.8 months) to that in the placebo or observation group (23.5 months) (HR, 0.48; 95% CI, 0.41 to 0.55). The median OS was not reached for the lenalidomide maintenance group and 86.0 months for the placebo or observation group (HR, 0.75; 95% CI, 0.63 to 0.90; P = 0.001). Thus, a significant improvement by lenalidomide maintenance compared with placebo or observation after ASCT in patients with newly diagnosed MM (NDMM) was confirmed in both PFS and OS. Moreover, the occurrence rates of a second primary malignancy (SPM) before PD were higher in group with lenalidomide maintenance than with placebo or observation group, whereas the occurrence rates of progression, death, or death due to myeloma were higher in placebo or observation group than group with lenalidomide maintenance. Therefore, the clinical use of lenalidomide as a maintenance therapy after ASCT should be performed with informed consent and adequate information on the benefits and risks, including SPM.

In the part for transplant eligible patients of Myeloma XI study, lenalidomide maintenance therapy until PD or observation was randomized 3 months after ASCT[15]. PFS in lenalidomide maintenance was superior to that in observation for high-risk patients (HR, 0.50; 95%CI, 0.35 to 0.70, p < 0.0001) as well as those who were MRD negative at the start of maintenance therapy (HR, 0.72; 95%CI, 0.55 to 0.95, p = 0.022).

As a clinical trial of lenalidomide maintenance therapy for transplant-ineligible patients, MM-015 compared MPR (melphalan, prednisolone, and lenalidomide) with lenalidomide maintenance therapy and MPR or MP alone in transplant-ineligible patients[16]. PFS was significantly improved in MPR with lenalidomide maintenance therapy (MPR-R) compared with MPR or MP; however, OS was comparable between MPR-R and MPR. The superiority of MPR-R to MPR or MP alone in PFS was especially evident in 65-75-year-old patients.

The FIRST trial compared the efficacy and safety of Rd (lenalidomide and dexamethasone) until PD (Rd continuous), Rd for 72 weeks (18 cycles; Rd18), and MPT (melphalan, prednisolone, and thalidomide) for 72 weeks (12 cycles) in transplant-ineligible NDMM patients[17]. The 4-year PFS was higher in Rd continuous (32.6%) than in Rd18 (14.3%). The median time to next treatment (TTNT) for Rd continuous was 30 months longer than that of Rd18 in patients achieving a complete or very good partial response (PR) (69.5 vs. 39.9 months).

Thus, elongation of PFS by lenalidomide maintenance therapy in transplant-ineligible patients is expected. The National Comprehensive Cancer Network (NCCN) guideline (Version 3.2023) describes lenalidomide as a preferred maintenance therapy (category 1) (https://www.nccn.org/guidelines/category_1). However, the median OS was comparable between Rd continuous and Rd18. Therefore, lenalidomide maintenance therapy after 19 cycles should be performed considering the benefits and risks, including toxicity (SPM).

Bortezomib

Bortezomib is the first clinically introduced proteasome inhibitor. Some clinical trials were performed on bortezomib maintenance therapy for transplant-eligible or ineligible patients.

HOVON-65/GMMG-HD4 is a phase III clinical trial that compared two years of thalidomide maintenance therapy after vincristine, doxorubicin, and dexamethasone (VAD) induction and ASCT and two years of bortezomib maintenance therapy after bortezomib, doxorubicin, and dexamethasone (PAD) induction and ASCT[18]. PFS was significantly prolonged in the PAD with bortezomib maintenance group than the VAD with thalidomide maintenance group during the median follow-up 96 months. There was no increase in SPM by bortezomib maintenance compared with tha-

lidomide maintenance. The negative effects on prognosis of high-risk cytogenetic aberration deletion 17p13 and renal impairment on PFS and OS were overcome by the PAD group but not the VAD group. These results indicate that post-transplant maintenance with bortezomib could improve PFS in high-risk subgroups of MM patients.

The phase III trial GEM05MENOS65 compared bortezomib/thalidomide (VT), thalidomide (T), and α-2b interferon (α2-IFN) maintenance therapy for up to three years after ASCT[19]. Induction therapy before ASCT comprised thalidomide + dexamethasone/bortezomib + thalidomide + dexamethasone (TD/VTD) and vincristine + bis-chloroethylnitrosourea (BCNU) + melphalan + cyclophosphamide + prednisone/vincristine + BCNU + doxorubicin + dexamethasone/bortezomib (VBMCP/VBAD/B). 91, 88, and 92 patients were randomly assigned to VT, T, and α2-IFN, respectively. PFS was significantly improved by VT as compared by T and α2-IFN (50.6 vs. 40.3 vs. 32.5 months, P = 0.03) during a median follow-up of 58.6 months. OS was similar among the three groups, and moderate to severe PN was observed with VT and T.

A retrospective analysis of real-world data about the outcomes of maintenance therapy with lenalidomide or bortezomib after proteasome inhibitor- or IMiD-based induction and ASCT was performed[20]; 577 patients with NDMM undergoing ASCT between 2010 and 2015 in Mayo Clinic (Rochester) were analyzed. The number of patients who received no maintenance, lenalidomide maintenance, or bortezomib maintenance was 341, 132, and 104, respectively. The rate of high-risk cytogenetics by fluorescence in situ hybridization (FISH) was higher in patients receiving lenalidomide or bortezomib maintenance than in those without maintenance therapy. Lenalidomide maintenance improved PFS as compared with no maintenance, even in patients with International Staging System (ISS) stage III disease and high-risk cytogenetics. PFS was unchanged by bortezomib maintenance in the entire cohort but was improved in the high-risk cytogenetic patients.

The results of two clinical trials about bortezomib maintenance therapies for transplant-ineligible patients are reported. As previously described, phase III study compared the efficacy between nine cycles of VMPT followed by maintenance with VT and nine cycles of VMP treatment alone in NDMM patients ineligible for ASCT[9].

In the GEM2005MAS65 trial, the efficacy and safety of maintenance therapy with VT or bortezomib plus prednisolone (VP) after six cycles of VMP or VTP (bortezomib + thalidomide + prednisolone) induction therapy in patients ≥ 65 years were analyzed[21]. The CR rate of VT after induction was 24%, which increased to 46%, while that of VP was 39%. The median PFS for VT (39 months) was higher than that for VP (32 months). The 5-year OS was also higher in VT (69%) than in VP (50%), although the differences did not reach statistical significance. The incidence of grade 3-4 PN was higher in VT (9%) than in VP (3%).

Thus, VT maintenance therapy for patients with MM who are ineligible for ASCT should be administered with caution because of the possible side effects.

Ixazomib

Ixazomib is the only oral proteasome inhibitor indicated for patients with MM. Ixazomib is approved as a drug for maintenance therapy and is expected to prolong disease-free duration (The 5th Guideline for Treatment, Japanese Society of Myeloma)[1].

TOURMALINE-MM3 is a double-blind, randomized, placebo-controlled phase III trial that examined the efficacy and safety of ixazomib maintenance therapy after ASCT[22]. Patients who achieved at least PR after induction therapy with proteasome inhibitors or IMiDs and received ASCT with a single high-dose melphalan therapy were targeted. They were randomly distributed to the ixazomib- or placebo-treated group for up to two years (ixazomib:placebo 3:2). Ixazomib treatment was started from 3 mg and increased to 4 mg from the 5th cycle if 3 mg of ixazomib is tolerable; 89% of patients received proteasome inhibitors during induction therapy. During a median of 31 months of observation, the median PFS was 26.5 months in the ixazomib group and 21.3 months in the placebo group (HR, 0.72; 95% CI, 0.58-0.89; P = 0.0023). Ixazomib maintenance therapy improved the PFS in patients ≥ 60 years and patients with ISS III. In patients with high-risk cytogenetics, including del(17p), t(4;14), and t(14;16), detected by FISH, achievement of 2-year PFS was better in the ixazomib group (46%) than the placebo

group (24%). PFS improvement by ixazomib maintenance therapy was independent of proteasome inhibitors in induction therapy. These improvements in efficacy were achieved by maintenance therapy within a fixed duration of two years.

Regarding the merit of ixazomib maintenance therapy in high-risk patients, the t(4;14) translocation in relapsed/refractory MM (RRMM) patients displayed shorter median PFS of Ld (12.0 months) as compared with that of ixazomib with Ld (18.5 months) (HR, 0.645; 95% CI, 0.250 to 1.6639)[23]. A retrospective analysis of survival in the context of chromosomal abnormalities for Ld-treated patients with RRMM displayed that median PFS was 13.0 months in 16 patients with t(4;14)[24]. In addition, Ld-treated patients with RRMM with del (13) and t(4;14) chromosomal abnormalities had lower overall response rates (ORRs) and shorter median PFS and OS as compared with those without these abnormalities[25].

Regarding safety, thrombocytopenia as a hematological adverse event and gastrointestinal disorders, such as nausea, diarrhea, and vomiting, were more common with ixazomib than with the placebo. Ixazomib maintenance therapy did not increase the rate of SPMs compared with the placebo. The incidence of adverse events resulting in discontinuation of the study drug was 7% and 5% in the ixazomib and placebo groups, respectively. Discontinuation due to adverse events in the meta-analysis of lenalidomide maintenance therapy after ASCT occurred in 29% of the lenalidomide maintenance group and 12% of the placebo or observation group[13]. Thus, continuing maintenance therapy might be easier with ixazomib than with lenalidomide. Based on the above clinical data, the NCCN guideline (Version 3.2023) has recommended ixazomib as a regimen for maintenance therapy (category 2B) (https://www.nccn.org/guidelines/category_1).

Ixazomib maintenance therapy was approved for patients without ASCT history in 2021 in Japan because of the results of the TOURMALINE-MM4 trial[26]. TOURMALINE-MM4, a phase III, double-blind, placebo-controlled study, randomly assigned transplant-ineligible patients into two groups: 425 patients received ixazomib, and 281 received placebo (3:2). The median PFS was 17.4 and 9.4 months in the ixazomib and placebo groups, respectively (HR, 0.659; 95%CI, 0.542 to 0.801; $P < 0.001$). Ixazomib improved the median PFS compared to the placebo in patients who achieved complete or very good PR postinduction (25.6 vs. 12.9 months; HR, 0.586; 95%CI, 0.449 to 0.765; $P < 0.001$). According to the evaluation of toxicity, the rate of grade 3/4 treatment-emergent adverse events (TEAEs) was 36.6% (ixazomib) and 23.2% (placebo); 12.9% of patients in the ixazomib group and 8.0% in the placebo group discontinued treatment because of TEAEs. As TEAEs, nausea (26.8% vs. 8.0%), vomiting (24.2% vs. 4.3%), and diarrhea (23.2% vs. 12.3%) were common. The incidence of SPMs was 5.2% in the ixazomib group and 6.2% in the placebo group; there was no remarkable increase in SPMs by ixazomib maintenance therapy.

The dynamics of minimal residual disease (MRD) detected by flow cytometry in 1280 transplant-eligible and ineligible patients from the TOURMALINE-MM3 and -MM4 trials were analyzed[27]. The risk of PD depended on the conversion from MRD− to MRD+ or from MRD+ to MRD− status during ixazomib or placebo maintenance. The 2-year PFS rate of patients converting from MRD+ to MRD− status was 76.8%, higher than that of patients with persistent MRD+ status (27.6%). The 2-year PFS rate of patients converting from MRD− to MRD+ status (34.2%) was lower than that of patients with sustained MRD− status (75.0%). Furthermore, the merit of ixazomib maintenance for PFS was observed in patients who were MRD+ before maintenance and at a 14-month landmark analysis. Thus, monitoring MRD for evaluation of the prognosis of ixazomib maintenance therapy in transplant-eligible and ineligible patients is suggested.

In the study of real-world data about costs for French patients with MM indicated that monthly costs necessary for patients with MM was twice in those who received 5 and more line of therapy (LOT) as compared in those who received up to 2 LOT[28]. Thus, possible disease control by the fixed duration of ixazomib maintenance therapy after induction therapy will be helpful to reduce the financial burden of treatment on patients.

Daratumumab

Daratumumab is a therapeutic antibody targeting CD38 in myeloma cells. CASSIOPEIA, a two-part,

open-label, randomized, phase 3 trial of transplant-eligible NDMM patients[29]. In part 1, patients were randomly assigned to daratumumab with VTD (D-VTD) or VTD-induction and consolidation therapy. In part 2, patients who achieved PR or better were randomly assigned to daratumumab maintenance therapy every 8 weeks or observation up to 2 years. The risk of PD or death was significantly reduced by daratumumab maintenance as compared with observation (HR, 0.53; 95% CI, 0.42-0.68; $p < 0.0001$).

Combination Therapy

As a maintenance therapy, the combination of ixazomib and lenalidomide after ASCT was investigated[30]. Sixty-four patients were enrolled in the study, and maintenance therapy was started within 60-180 days of stem cell infusion. Combination therapy was performed in each 28-day cycle. The starting dose of lenalidomide was 10 mg/day orally for 28 days, with the option to increase the dose to 15 mg after three cycles, according to the treating physician's discretion. Ixazomib 3 mg (n = 48 patients) or 4 mg (n = 16 patients) was orally administered on days 1, 8, and 15 of each 28-day cycle. Improvement in response rates over time from baseline post-ASCT was observed in 39 patients. The CR/stringent CR rate was 43%, and the median PFS for all patients was 73 months, which was not reached in patients with ISS stage I disease. The median PFS of patients with ISS stage I (n = 33), III (n = 9), and high-risk cytogenetics (n = 14) was not reached, 34 and, 25 months, respectively. Subgroup analysis of PFS based on the ISS stage at diagnosis and revised ISS stage did not demonstrate statistically significant differences between the groups. The median OS was not reached with a median follow-up of 62 months (range, 25-82 months).

In addition to the efficacy and safety of carfilzomib-based induction and consolidation therapies with or without transplantation for NDMM patients, the efficacy and safety of maintenance treatment with carfilzomib plus lenalidomide versus lenalidomide alone were evaluated in the UNITO-MM-01/FORTE study, a randomized, open-label, phase II trial[31]. Patients were randomly assigned (1:1:1) to four cycles of carfilzomib, lenalidomide, and dexamethasone (KRd) induction plus high-dose melphalan and ASCT followed by four 28-day KRd consolidation, KRd12 (12 cycles of 28-day KRd) or four cycles of carfilzomib, cyclophosphamide, dexamethasone (KCd) induction plus ASCT followed by four cycles of 28-day KCd consolidation. Four hundred and seventy-four patients were enrolled (158 to KRd plus ASCT, 157 to KRd12, and 159 to KCd plus ASCT). The rate of at least very good PR was 70% in the KRd group and 53% in the KCd group (odds ratio (OR), 2.14; 95% CI 1.44-3.19, P = 0.0002) with a median follow-up duration of 50.9 months from the first randomization. TEAEs were reported in 11% of the KRd-ASCT, 19% of the KRd12, and 11% of the KCd plus ASCT groups; the most common serious adverse event was pneumonia, which occurred in 4% of the KRd-ASCT, 3% of the KRd12, and 3% of the KCd plus ASCT groups. As a maintenance therapy, 178 patients received carfilzomib plus lenalidomide, and 178 received lenalidomide alone. The 3-year PFS was 75% with carfilzomib plus lenalidomide and 65% with lenalidomide alone (HR, 0.64; 95% CI 0.44-0.94, P = 0.023) with a median follow-up duration of 37.3 months from the second randomization. The most common grade 3-4 adverse events during maintenance therapy were neutropenia (20% of carfilzomib plus lenalidomide vs. 23% of lenalidomide alone), infections (5% vs. 7%), and vascular events (7% vs. 1%). One death occurred due to TEAE in the carfilzomib plus lenalidomide maintenance group. These results indicate the superiority of carfilzomib plus lenalidomide as maintenance therapy to lenalidomide alone, with a comparable safety profile between these regimens.

The usefulness of combination therapy as a maintenance therapy in high-risk patients must be evaluated in future studies.

Ixazomib-maintenance Therapy for Transplant-ineligible Patients Intolerant to Lenalidomide (IMTIL) Study (UMIN000048285)

In medical practice, strategies to choose the drug for maintenance therapy are determined for transplant-eligible and transplant-ineligible patients. In this regard, we suggest that ixazomib maintenance therapy will benefit patients intolerant to lenalidomide. We commenced a multi-center prospective clinical trial to determine the efficacy and safety of ixazomib mainte-

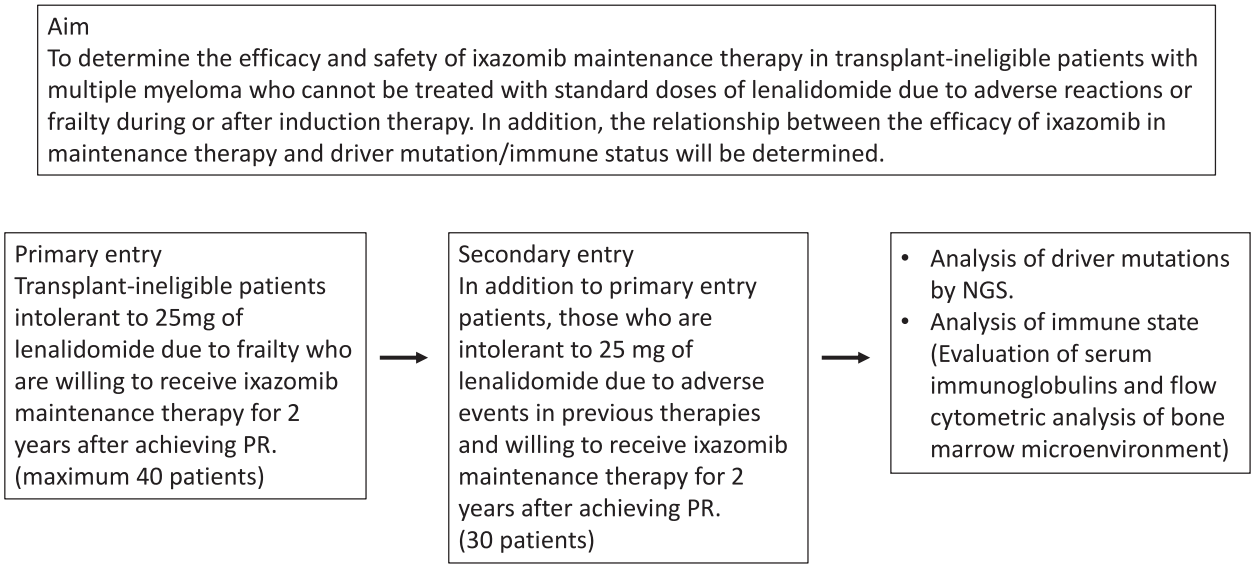

Figure 3 Outline of ixazomib maintenance therapy for transplant-ineligible patients intolerant to lenalidomide (IMTIL) study (UMIN000048285).

PR, partial response; NGS, next-generation sequencing

nance therapy in transplant-ineligible patients with MM who cannot be treated with standard doses of lenalidomide due to adverse reactions or frailty during or after induction therapy (Fig. 3). We will also investigate the relationship between the efficacy of ixazomib in maintenance therapy and driver mutation and immune status in the bone marrow microenvironment of patients with MM.

This study consists of a two-stage registration to secure the enrollment of 30 patients for ixazomib maintenance therapy. Primary registration (up to 40 patients) will comprise two criteria: (1) Transplant-ineligible patients who cannot tolerate a standard dose of lenalidomide due to frailty; (2) Patients are scheduled to receive ixazomib maintenance therapy for two years after achieving at least a PR to induction therapy. Secondary registration will consist of patients initially enrolled and those who cannot be treated with standard doses of lenalidomide due to adverse reactions during or after induction therapy and before starting ixazomib maintenance therapy for two years (planned enrollment: 30 patients).

In a previous study, we demonstrated that driver mutations, such as NRAS, KRAS, and TP 53 mutations in cell-free DNA from peripheral blood, are sensitive biomarkers for diagnosing relapse[32]. Analysis of the dynamics of clones with driver mutations in tumor cells during and following ixazomib maintenance therapy will help elucidate whether deep responses and true MRD negativity can be achieved with ixazomib maintenance therapy. The relationship between the survival of patients with myeloma and immune status also showed that patients with high expression of the natural killer (NK) cell-activating receptor NKG2D ligand MICA/MICB, ULBp- 2/5/6 on myeloma cells have a better prognosis[33]. Furthermore, suppression of antitumor immunity by immune checkpoints, such as PD-1 and TIGIT expressed on cytotoxic T cells, has attracted attention[34]. The impact of the expression of these immune-related molecules on the therapeutic effect of ixazomib maintenance therapy is unknown, and its elucidation will help to identify effective cases of ixazomib maintenance therapy.

Conclusion

Each drug for maintenance therapy has specific characteristics as described in Fig. 4. The role of maintenance therapy in MM is to inhibit disease progression after induction therapy with the minimum physical and financial burden for patients. Furthermore, making therapeutic antibody and IMiDs free duration will expand the treatment options for patients who become relapse/refractory to the maintenance therapy. Personalized maintenance therapy based on the cyto-

Drug	
Thalidomide	Transplant-eligible patients Progression-free survival (PFS) was improved in the six randomized control trials (RCTs) of thalidomide maintenance therapy after auto stem cell transplantation (ASCT). Overall survival (OS) was elongated in two trials by maintenance therapy. However, it is not considered a standard therapy due to adverse effects. Transplant-ineligible patients PFS was improved in thalidomide maintenance therapy in transplant-ineligible patients; however, it is unclear if OS was improved. Furthermore, adverse events frequently occurred in elderly patients. Therefore, thalidomide as a maintenance therapy in transplant-ineligible patients should be administered with caution.
Lenalidomide	PFS was improved in lenalidomide maintenance therapy in patients after ASCT and transplant-ineligible patients. The merit of OS in lenalidomide maintenance therapy is unclear. In clinical settings, the use of lenalidomide as a maintenance therapy should be performed with careful consideration of the benefits and risks. Secondary primary malignancies (SPMs) before myeloma disease progression occurred more frequently in lenalidomide maintenance than in placebo in the meta-analysis of three RCTs. Therefore, informed consent should be obtained after explaining the merits and risks of lenalidomide maintenance therapy before commencing the treatment.
Bortezomib	No RCTs have estimated the effect of bortezomib maintenance therapy. Bortezomib maintenance therapy after ASCT for high-risk patients may improve the prognosis of these patients. Bortezomib plus thalidomide maintenance therapy after induction therapy for transplant-ineligible patients may improve their prognosis.
Ixazomib	Ixazomib maintenance therapy after ASCT improves PFS and is approved in Japan. The risk of SPMs did not increase in the RCT of ixazomib maintenance therapy after ASCT. Ixazomib maintenance therapy was approved for patients without ASCT history in Japan based on the results of the TOURMALINE-MM4 trial.

Figure 4 Summary of maintenance therapy with a single agent for patients with MM.

genetic risk of MM and the frailty of patients will help improve the prognosis of patients with MM.

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