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Clinical Study Protocol

Phase II Study of Treatment for Newly Diagnosed Multiple Myeloma Patients Over 75 Years Old with Alternating Bortezomib/dexamethasone and Lenalidomide/dexamethasone: the MARBLE Trial

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Elderly multiple myeloma (MM) patients, who are generally ineligible for transplantation, have high risks of death and treatment discontinuation, and require a regimen incorporating novel agents that balance safety, tolerability, and efficacy. We evaluated alternating bortezomib-dexamethasone and lenalidomide-dexamethasone treatments administered over a 63-day cycle in transplant-ineligible elderly patients with newly diagnosed MM. Subcutaneous bortezomib 1.3 mg/m^2 was administered weekly on Days 1, 8, 15, and 22; oral lenalidomide 15 mg daily on Days 36-56; and oral dexamethasone 20 mg on Days 1, 8, 15, 22, 36, 43, 50, and 57 for 6 cycles. The primary endpoint was the overall response rate.

Key words: bortezomib, lenalidomide, dexamethasone, myeloma

Multiple myeloma (MM) is caused by tumorigenically transformed plasma cells, a terminally differentiated form of B lymphocytes, and is characterized by the production of an abnormal protein called monoclonal immunoglobin (M-protein) by tumor cells. Even in the novel agent era this disease is intractable, and it exhibits serious clinical symptoms, including hypercalcemia, renal insufficiency, anemia, and bone osteolytic changes (the so-called CRAB criteria) [1].

Nonetheless, drastic improvements in therapeutic outcomes have been achieved by treatment with high-dose melphalan plus autologous stem cell transplantation (ASCT), as well as by novel agents such as bortezomib, lenalidomide, and thalidomide. However, these treatments have failed to improve long-term survival in elderly patients, who are generally ineligible for ASCT. Thus, the greatest benefits of these treatments are limited to patients younger than 70 years, mainly owing to adverse events (AEs) [2]. Moreover, the European Myeloma Network recommends reducing the dosage of various agents based on a patient's age and other risk factors [3].

The two following options are recommended for elderly patients based on data from randomized phase

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III trials: bortezomib [intravenous (iv)]/melphalan/prednisone (BMP), based on the VISTA trial [4], and lenalidomide plus low-dose dexamethasone (Ld), based on the FIRST trial [5]. In Japan, both BMP and Ld have been approved in frontline settings.

The VISTA trial reported that, compared with conventional melphalan-prednisone therapy, treatment with BMP significantly extended progression-free survival (PFS) and overall survival (OS). However, BMP therapy was associated with a high incidence of AEs of grade 3 and higher, and only 59% of the treatment groups completed all nine cycles of the regimen [4]. Combination therapy with bortezomib-dexamethasone (BD) has also been examined, notably by the UPFRONT trial, a US community-based phase IIIB study designed to compare three front-line bortezomib(iv)-based regimens in ASCT-ineligible patients with MM. Outcomes in elderly MM patients (median age 73 years) were compared among BD, BMP, and BD plus thalidomide (BTD) [6] groups. Analysis conducted at a median of 42.7 months showed no significant differences in PFS among all treatments. BMP was associated with the highest rate of hematologic toxicity, whereas peripheral neuropathy (PN) of grade ≥ 2 was reported in 47% of the BTD arm of the study. The rates of AEs and discontinuations due to AEs appeared higher with BTD than with BD or BMP. These findings suggested that a BD regimen in which bortezomib is administered twice weekly is a treatment option with balanced efficacy and safety for elderly MM patients [6]. Likewise, modifying the frequency of bortezomib administration in BMP therapy to once per week has been shown to reduce toxicity and discontinuation while maintaining efficacy, as shown by other trials conducted in Italy (GIMEMA) [7] and Spain (PETHEMA) [8]. Meta-analysis of the data of 1435 individual patients enrolled in 4 European phase III trials (GISMM-2001, HOVON 49, GEM05MAS, and GIMEMA MM0305) involving thalidomide and/or bortezomib(iv) indicated that an age of ≥ 75 years and treatment discontinuation due to AEs have significant negative impacts on the survival of elderly patients [9]. To improve outcomes in elderly patients aged ≥ 75 years, the development of a treatment that can further reduce toxicity and discontinuation is necessary.

Based on the results of an open-label, randomized MMY-3021 phase III study comparing subcutaneous (sc) and iv administration of bortezomib, sc bortezomib administration is safe and effective [10]. Currently, once-a-week sc administration of bortezomib is widely used in clinical practice.

The FIRST trial compared the combination of melphalan-prednisone-thalidomide (MPT) versus Ld for 18 cycles and MPT versus Ld until progression (PD) in 1623 patients with ASCT-ineligible, newly diagnosed multiple myeloma (NDMM) [5]. PFS was higher in the PD arm than in the other 2 arms, and OS was higher in the PD arm than in the MPT arm. Based on the results of the trial, the lenalidomide plus high-dose dexamethasone (LD) regimen is considered the new standard of care for patients with NDMM who are unable to tolerate triplet therapy owing to advanced age, poor performance status, or comorbidities. In contrast, the discontinuation rate in the PD arm was 87%, with 51% discontinuation due to disease progression and 12% due to AEs, thereby showing the difficulty of achieving a sustained therapeutic effect with a single novel agent.

To further optimize treatment outcomes in this patient population, a triplet combination of bortezomib plus LD (LBD) administered using a modified dose and schedule (LBD-lite) was evaluated [11]. The LBD-lite regimen consisted of a 35-day cycle of lenalidomide (15 mg, Days 1-21) plus once a week sc administration of bortezomib and dexamethasone. A total of 53 NDMM patients were enrolled, with a median age at diagnosis of 73 years. The majority of patients experienced treatment-related AEs, including fatigue (74%) and PN (62%), but these AEs were mostly of grade 1/2 severity. The investigator-reported overall response rate (ORR) was 86%, including 66% ≥ very good partial response (VGPR). After a median follow-up of 30 months, the median PFS was 35.1 months, whereas the median OS had not been reached. Among the 36% of patients who discontinued therapy prior to completion, 12% had progressive disease, 4% showed treatment toxicity, and 2% switched to non-protocol therapy. On the basis of these results, modified LBD was considered to be a tolerated and effective option for elderly ASCT-ineligible NDMM patients.

Currently, although the benefits of these novel agents have become clear, the majority of patients die after a series of relapses. An analysis of molecular abnormalities associated with onset and progression using next-generation sequencing revealed that subclonal diversity was found even at diagnosis and showed progression using the Darwinian branching model [12]. Therapeutic approaches that depend on a single-class

treatment result in the proliferation and domination of a minor clone in the tumor population. Therefore, at the induction therapy, entire clones of myeloma cells must be suppressed by combining agents with different mechanisms. Furthermore, their continuous administration may also be essential.

There is little evidence supporting the strategy of using alternating chemotherapy regimens to treat MM. Sequential and alternating regimens with BMP and Ld have recently been compared in GEM2010MAS65, an international phase II trial, which hypothesized that the alternating strategy would minimize the emergence of resistant clones and would reduce the cumulative toxicity [13]. A total of 242 patients were randomized to receive a sequential regimen consisting of 9 cycles of BMP followed by 9 cycles of Ld or the same regimens in an alternating approach. After a median follow-up of 27 months, the median PFS was 30 months in both the sequential and alternating arms (p = not significant), whereas the median OS had not been reached. No significant differences in the frequency of the toxicity profile were observed between the 2 arms, but all early deaths and 71% of early discontinuations occurred in patients aged ≥ 75 years. Considering the results of this trial, alternating treatment for patients aged ≥ 75 years needs to be optimized, such as through dose modification of the agents, the use of a fixed period, and the exclusion of alkylators or the use of alkylator-free regimens.

In our trial, we evaluated alternating Bd and Ld (alkylator-free regimen) and investigated the regimen with balanced safety, tolerability, and efficacy in elderly patients with ASCT-ineligible NDMM. Moreover, we analyzed chromosomal abnormalities in the patients by fluorescence *in situ* hybridization (FISH), and examined whether the alternating strategy suppresses clonal evolution.

Trial design. In this phase II, open-label, single-arm, multicenter trial, we evaluate the efficacy and safety of alternating Bd and Ld as an induction therapy for NDMM patients older than 75 years (who are ineligible for ASCT). This trial was approved by the Central Ethics Review Committee for Clinical Research of the National Hospital Organization on 20 July 2014 (H26-0320002). This study has been registered in the Clinical Trial Registry (UMIN-CTR) (UMIN000013773).

Endpoints

Primary endpoints. ORR during the period of administration of chemotherapy alternating between Bd and Ld: proportion of eligible patients whose best responses were a stringent complete response, complete response (CR), VGPR, and partial response (PR). The response is evaluated according to the International Myeloma Working Group Uniform Response Criteria [14].

Secondary endpoints

- AEs
- Proportion of treatment continuation: the proportion of patients who have continued the study treatment for up to 6 cycles without discontinuation due to AE or progression of disease among enrolled patients.
- CR rate: proportion of eligible patients whose best response was a CR.
- VGPR: proportion of eligible patients whose best response was a VGPR.
- PFS: duration from the start of treatment to the first event of progression, relapse, or death due to any cause. Patients who survive without progression are censored at the last day for which no progression was confirmed.
- OS: duration from the start of treatment to death due to any cause. Patients who survive are censored at the last day of confirmed survival.
- Time to response (TTR): duration from the start of treatment to the first response above PR. Patients without a response above PR are censored at the following events: 1) the longest follow-up period in patients with progression, and 2) the last evaluation date in patients without progressive disease and relapse.

Eligibility Criteria

Inclusion criteria

1. Patients aged older than 75 years.
2. Patients with symptomatic MM newly diagnosed by the WHO criteria, and who are ineligible for ASCT.
3. Patients with measurable disease: an M-protein level ≥ 0.5 g/dL for IgG, IgA, or IgM type myeloma; an M-protein level ≥ 0.05 g/dL for IgD type myeloma; or urinary M-protein excretion ≥ 200 mg/24-h.

4. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, or 3 owing to osteolytic lesions alone.
5. Patients who meet the following criteria of the pretreatment clinical laboratory parameters:
   - Transaminases (AST, ALT) < 3.0 × the upper limit of normal
   - Creatinine clearance ≥ 30 mL/min
   - Absolute neutrophil count ≥ 1.0×10^9/L
   - Platelet count ≥ 50×10^9/L
   - Ejection fraction ≥ 50%
   - PaO2 ≥ 60 mmHg or SpO2 ≥ 93%
6. Patients who agree to register for the Revision of Procedures for Appropriate Management of Revlimid® and Pomalyst® (RevMate®), and comply with the contents.
7. Patients who were notified of and provided with a sufficient explanation of the contents of this study, and who then provide consent in writing to participate in the study by their free will.

Exclusion criteria

1. Patients with plasma cell leukemia, cardiac amyloidosis, or POEMS syndrome.
2. Patients who have PN of grade ≥ 2.
3. Patients who have uncontrolled liver dysfunction, renal dysfunction, heart failure, impaired respiratory function, diabetes, or hypertension.
4. Patients with concurrent tuberculosis, herpes simplex keratitis, systemic fungal disease, or active infection.
5. Patients who have had a recent operation.
6. Patients who have had a myocardial infarction within 6 months of enrollment or deep vein thrombosis/pulmonary embolism within 3 years.
7. Patients who have active and advanced double cancer (simultaneous or within 5 years post-remission).
8. Patients who are positive for hepatitis B antigen, hepatitis C antibody, or HIV antibody.
9. Patients with pneumonitis (interstitial pneumonia) or pulmonary fibrosis in clinical practice, or with abnormal (high-resolution) chest CT findings in the bilateral lungs regardless of the presence or absence of symptoms.
10. Patients with hypersensitivity to boron or mannitol.
11. Patients with psychiatric diseases or psychological symptoms.
12. Patients otherwise judged inappropriate to participate in this study.

Treatment Methods

Interventions. Patients will be enrolled in the trial within 4 weeks of diagnosis and begin treatment according to the protocol shown in Fig. 1. A physician will decide whether each patient will receive treatment in an inpatient or outpatient setting.

Patients will receive Bd therapy from Days 1-35 (for 35 days), and Ld therapy from Days 36-63 (for 28 days). Patients will undergo a total of six treatment cycles, with each cycle consisting of a 63-day regimen, as mentioned above. The starting doses of bortezomib and lenalidomide will be adjusted on the basis of the patients' age, general condition, and renal function. The scheme of this study is shown in Fig. 2

Bd therapy. Patients will be administered sc bortezomib 1.3 mg/m^2 and oral dexamethasone 20 mg on Days 1, 8, 15, and 22. The site of bortezomib administration will be rotated between sessions to avoid consecutive injections at the same site (*e.g.*, the left thigh, right thigh or abdomen). Operators will pull the

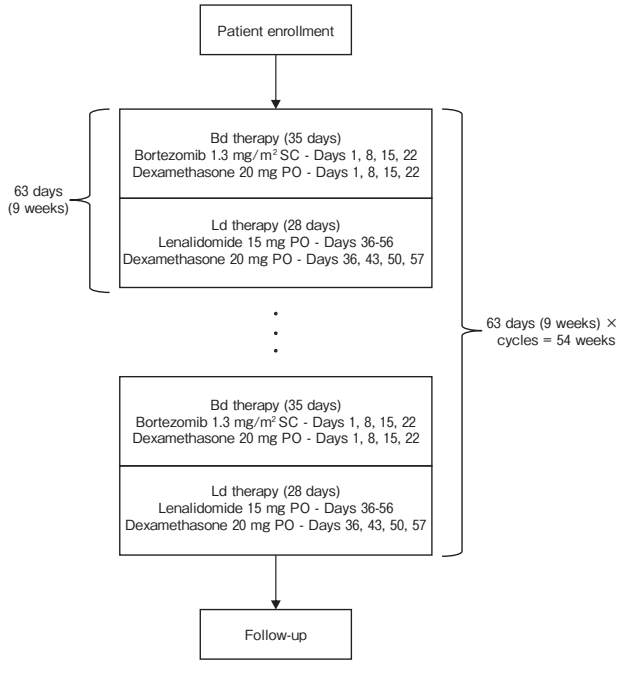

Fig. 1 Study design.
PO, by mouth (*per os*); SC, subcutaneous injection.

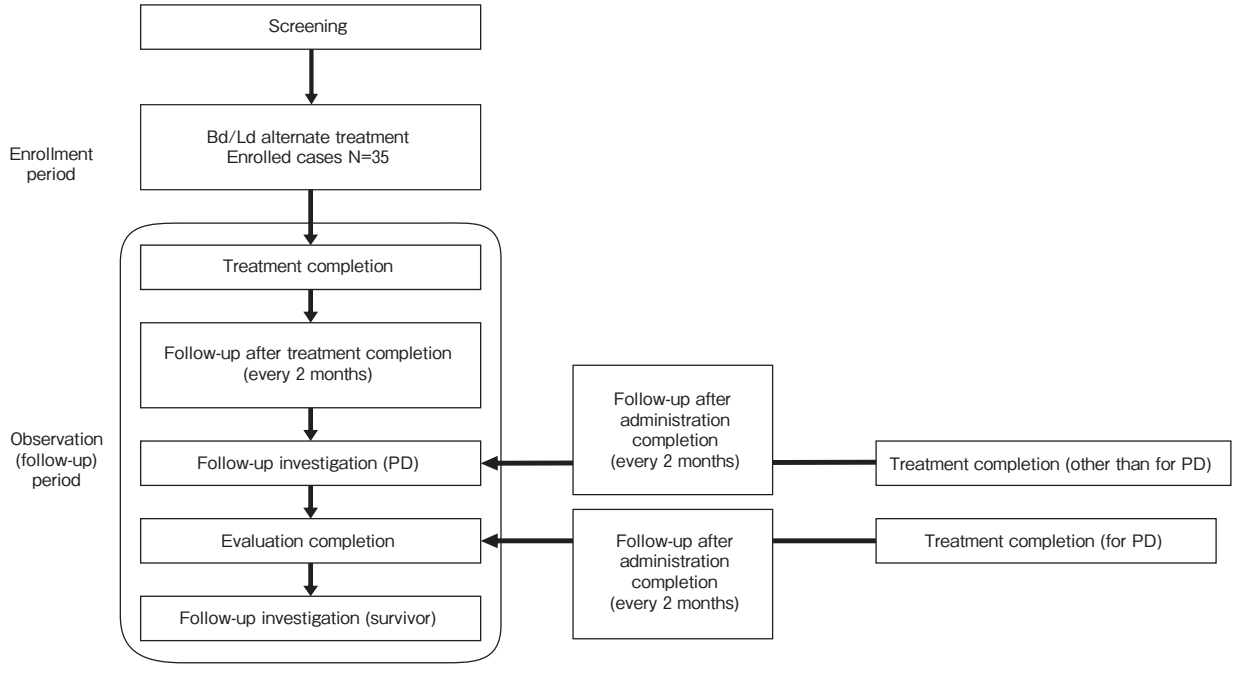

Fig. 2 Study schema

syringe plunger back slightly after insertion to verify the absence of regurgitation, ensuring that nerve damage is avoided.

Bortezomib administration will be suspended upon observation of non-hematologic (grade 3+; except for PN and neuropathic pain) or hematologic AE (grade 4), as defined by the Common Terminology Criteria for Adverse Events (ver. 4.0). Patients who recover will resume administration at a reduced dose. Bortezomib administration will be discontinued and patients will be withdrawn from the trial if these AEs fail to subside, or if an AE recurs even with the minimum dose. In addition, the dosage will be lowered in the event of PN or neuropathic pain. If a patient experiences fluctuation in body weight of ± 5 kg or greater after the start of treatment, their body surface area will be remeasured to recalculate the appropriate dose.

Dexamethasone may be suspended or administered at a reduced dose at the physician's discretion if an AE occurs.

Ld therapy. Following Bd therapy, patients will be administered lenalidomide 15 mg on each of Days 36-56 and dexamethasone 10 mg on Days 36, 43, 50, and 57.

The lenalidomide dosage will be reduced in patients with poor renal function (including at the initial dose). Moreover, the lenalidomide dosage will also be reduced (or suspended) if an AE occurs.

If an AE occurs in Bd therapy, dexamethasone may be suspended or administered at a reduced dose at a physician's discretion.

Statistical Considerations

Sample size. One trial reported that Ld therapy achieved an ORR of 70.4% in untreated MM patients aged 75 years or older [15]. On the other hand, the EVOLUTION study observed ORRs of 85% and 88% for bortezomib-lenalidomide-dexamethasone and bortezomib-dexamethasone-cyclophosphamide-lenalidomide therapies in a population of untreated MM patients [16]. We expect our alternating bortezomib and lenalidomide approach to achieve an ORR of 88%. Our necessary sample size was calculated to be $n = 32$, assuming an expected response rate of 88%, a threshold response rate of 70.4%, $\alpha = 0.05$ (one-sided), and $\beta = 0.2$ (80% power), based on a binomial distribution. We set the sample size at 35 assuming a dropout rate of 10%.

Statistical methods. ORR, CR rate, and VGPR will be estimated with 90% confidence intervals (CI). Survival curves of PFS, OS, and TTR will be calculated using the Kaplan-Meier method; CI will be calculated

using Greenwood's formula. Occurrences of worst-grade AEs, grade-3+ AEs, and serious AEs will be calculated.

Discussion

Trial participants, while being monitored for signs of relapse, will be administered alternating chemotherapy with two agents with different mechanisms currently considered effective in treating MM: the proteasome inhibitor bortezomib and the immunomodulator lenalidomide. Our objective is to investigate whether these drugs can achieve acceptable safety and efficacy in elderly MM patients. Chromosomal analysis will also be conducted to determine whether this alternating strategy proves useful in preventing clonal evolution.

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