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Review Article

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Review Article

Recent advances in the management of older adults with newly diagnosed multiple myeloma in Japan

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Abstract

Multiple myeloma is a cancer of plasma cells; the incidence rate of multiple myeloma is high among older adults. Although significant advances have been made in the clinical management of multiple myeloma driven by the introduction of novel drugs, such as proteasome inhibitors, immunomodulators and antibodies, multiple myeloma remains incurable. Hence, the current therapeutic goal for multiple myeloma is to achieve long-term survival while maintaining a good quality of life. In this context, personalized treatment to balance the efficacy and safety of therapies is important, especially for older adults as they display diverse physical, cognitive or organ functioning. Furthermore, old age is also often associated with frailty. Several tools for evaluating frailty in older adults with multiple myeloma are now available, and frail patients defined by these tools have shown a poor prognosis and more treatment-related toxicities. In addition, it is important to evaluate other factors, such as the International Staging System, high-risk chromosomal abnormalities and treatment response, to predict the clinical course of patients. Further investigations are required to determine how these factors can optimize the treatment for multiple myeloma. In this review, we present a detailed account on the developments and issues related to the current treatment approaches for older adults with newly diagnosed multiple myeloma. We also discuss the ongoing phase III clinical study conducted by the lymphoma study group of the Japan Clinical Oncology Group, which targeted older adults with newly diagnosed multiple myeloma.

Key words: multiple myeloma, treatment strategies, frailty, novel drugs

Introduction

Multiple myeloma (MM) is characterized by the proliferation of neoplastic plasma cells. It accounts for ∼1 and 10% of all malignancies and hematopoietic tumors, respectively (1). The incidence of MM is higher in older adults, and the median age at MM diagnosis is 67 years in the Japanese population. In 2018, ∼7700 individuals (4100 men and 3600 women) were diagnosed with MM in Japan (age-adjusted incidence of 6.1 per 100 000 individuals), and the morbidity is increasing with time (2). This also reflects the increase among older adults in Japan.

Although novel agents have been developed for the treatment of MM in recent years and the prognosis of patients has improved, the

disease remains incurable. Therefore, the therapeutic goal for MM is to achieve long-term survival with a good quality of life (1). Since older adults with MM display variations not only in the physical but also in cognitive or organ functions, it is difficult to apply a standard treatment regimen to all. The optimal treatment needs to balance the efficacy and safety in each patient.

This review discusses the development and issues associated with the management of older adults with newly diagnosed multiple myeloma (NDMM).

Evaluation of prognostic factors

Cytogenetic abnormalities

Cytogenetic abnormalities (CAs) have been associated with the prognosis of MM, with some of the CAs acting as representative disease-based prognostic factors. The International Myeloma Working Group (IMWG) defined translocation (t) and deletion (del) of chromosomes t(4;14), del(17/17p), t(14;16), t(14;20), non-hyperdiploidy and gain of chromosome (1q) as the high-risk CAs for MM (3); patients with these CAs have shorter median survival than those without the high-risk CAs. In particular, patients with MM having one or more of t(4;14), del(17p) and t(14;16) are recognized by the revised International Staging System (R-ISS) (4) and often constitute the high-risk subgroup in recent clinical trials. Gain or amplification of chromosome arm 1q (+1q) is one of the most common recurrent CAs in MM and is found in 30–40% of patients at diagnosis (3). Although +1q is often considered as a poor prognostic marker for MM, controversy still exists regarding the significance of the copy number of 1q; the adverse impact of +1q on the survival may be greater in patients with amplification of 1q (harboring at least four copies) than in those with a gain of 1q (3 copies) (5,6).

Fluorescence *in situ* hybridization (FISH) using a sample purified by CD138 sorting is the standard technique for evaluating CAs in MM; however, the treatment outcomes of patients with high-risk CAs in clinical trials should be cautiously interpreted because of the following limitations of the FISH analysis: (i) the optimal thresholds for predicting the poor prognosis of MM, especially del(17p) and + 1q, are not uniformly determined and may vary among various clinical trials; (ii) CD138 purification is not routinely performed for the FISH analysis in clinical practice in Japan and (iii) there may be discrepancies in the interpretation of the results of the FISH analysis due to interobserver differences between those performed in central and regional laboratories.

ISS and R-ISS

The ISS is a simple and reproducible three-stage classification based on a combination of serum $\beta 2$ microglobulin and albumin levels (7). The ISS was established based on the clinical and laboratory data of patients with NDMM before the introduction of proteasome inhibitors and immunomodulatory drugs in clinical practice. Therefore, although ISS is still the most widely used staging system for patients with MM, R-ISS, which combines ISS with the status of high-risk CAs and serum lactate dehydrogenase levels, is a more robust prognostic tool (4).

Recently, the prognostic impact of genetic alterations assessed by the next-generation sequencing (NGS) in combination with ISS was evaluated in a large repository of patients with NDMM (5). This study revealed that patients with ISS III plus amplification (not gain) of 1q21 and those with biallelic TP53 inactivation constitute an extremely poor prognostic subgroup, with a median overall survival (OS) of 20.7 months.

Frailty

Even within the same age group, heterogeneity in physical, cognitive and organ functions becomes more apparent in older patients, underscoring the importance of assessing these functions to understand frailty in older patients. Frailty is a typical patient-based factor for predicting the clinical course of older patients with MM. Representative tools utilized to analyze the frailty scores of the patients with MM are summarized in Table 1.

The IMWG proposed a scoring system using age, Katz activity of daily living (ADL), Lawton instrumental ADL (IADL) and Charlson Comorbidity Index (CCI) to evaluate frailty in patients with MM (8). This scoring system was developed from the pooled data of 869 older adults with NDMM enrolled in clinical trials. According to the score, patients were categorized as fit, intermediate-fit and frail. The 3-year OS was 84, 76, and 57% in fit, intermediate-fit [hazard ratio (HR), 1.61; $P = 0.042$] and frail (HR, 3.57; $P < 0.001$) patients, respectively. The prognostic impact of frailty score on the OS was similar even in different subgroups defined by the ISS and CAs. In addition, frail patients had significantly more adverse events (AEs) than fit patients.

Using performance status (PS) instead of ADL and IADL, a simplified frailty score using age, CCI and PS was developed from a supplementary analysis of the FIRST trial (9,10). Patients were classified into two groups (non-frail and frail groups), and those in the frail group had inferior outcomes, especially the OS.

The Myeloma Research Alliance risk profile (MRP) consists of not only geriatric domains (PS and age) but also disease-based factors (C-reactive protein and ISS) (11). The MRP was established from the data of transplant-ineligible (TI)-NDMM patients enrolled in the National Cancer Research Institute Myeloma XI trial (12) and was shown to be prognostic for the OS and progression-free survival (PFS). It also remained prognostic irrespective of the status of the high-risk CAs. The significance of the risk-adjusted treatment strategy determined by MRP is currently being evaluated in a randomized phase III study (NCT03720041).

Although frailty score is a widely accepted concept that should be considered in the treatment of older patients with MM, it is associated with following limitations: (i) inability of the frailty scores to highlight whether the observed physical function impairment is due to aging or co-morbidity (often irreversible) or MM symptoms, such as bone pain (possibly reversible) and (ii) in the IMWG and simplified frailty score, patients aged >80 years were automatically defined as frail regardless of their physical/physiological functioning. This may not truly represent the status of older adults who are otherwise fit, and (iii) currently, there is insufficient information to employ a frailty score-based approach; however, with further studies, this is expected to be the standard in the future.

Treatment strategies for older patients with NDMM

High-dose chemotherapy with autologous stem cell transplantation

Autologous stem cell transplantation (ASCT) is the standard of care for younger patients with NDMM. Historically, clinical trials have evaluated the significance of ASCT in which patients aged <65 years

Table 1. Representative tools for frailty evaluation of older patients with multiple myeloma (MM)

	IMWG frailty score (8)		Simplified frailty score (10)		MRP (11)	
	Parameter	Points	Parameter	Points	Parameter	Formula
Age	76–80	1	76–80	1	Age (in year)	(Age-74.4) * 0.0165
	>80	2	>80	2		
Performance/	Any ADL dependence	1	ECOG PS 1	1	WHO PS (0-4)	(PS-2) * 0.199
functional status	Any IADL dependence	1	ECOG PS ≥2	2		
Co-morbidities	CCI ≥2	1	CCI ≥2	1	—	—
Stage	—	—	—	—	ISS (1–3)	(ISS-2) * 0.212
Biomarker	—	—	—	—	C-reactive protein (mg/L)	[log(CRP + 1) – 2.08] * 0.0315
Total score	Fit	0	Non-frail	0–1	Low	<−0.256
	Intermediate fit	1	Frail	≥2	Medium	−0.256 to −0.0283
	Frail	≥2			High	> −0.0283
Outcome		3y OS		Median OS		Median OS
	Fit	84%	Non-frail	5.8y	Low	5y
	Intermediate fit	76%	Frail	3.3y	Medium	3.7y
	Frail	57%			High	2.1y

IMWG, International Myeloma Working Group; MRP, Myeloma Research Alliance risk profile; ADL, activities of daily living; IADL, instrumental activities of daily living; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; PS, performance status; CCI, Charlson Comorbidity Index; ISS, International Staging System; OS, overall survival.

were enrolled (13,14). Therefore, the guidelines of the Japanese Society of Hematology state that patients aged ≥65 years and/or with vital organ impairment are not candidates for ASCT (1). However, there is increasing evidence regarding the safety of ASCT in patients ≥65 years of age (15). Therefore, considering the fitness, ASCT may be performed in selected older patients at some institutions.

On the other hand, the treatment outcomes of TI-NDMM patients are improving owing to the development of effective novel therapies. When patients aged ≥65 years are considered for ASCT, it is important to discuss the merits and demerits of both the transplant and non-transplant treatment strategies with patients; furthermore, considering their preferences is just as important. Possibly, these patients benefit most from the standard of care provided for TI-NDMM patients, as discussed below.

The standard of care for TI-NDMM patients

Melphalan, prednisone and bortezomib (MPB) (16) or lenalidomide and dexamethasone (Ld) (17) were the standard of care therapy for TI-NDMM; continuous efforts have been made to improve the outcomes by introducing other novel drugs into these regimens. Table 2 shows the recommended induction regimens for TI patients with NDMM from the most recent treatment guidelines in Japan, Europe and the USA (18–20). Although slight differences in the recommendation levels were found between the guidelines, daratumumab plus MPB (D-MPB), daratumumab plus Ld (D-Ld) and bortezomib, lenalidomide and dexamethasone (BLd) are the standard regimens.

Daratumumab plus MPB. The ALCYONE randomized controlled trial (21) compared MPB (without maintenance therapy) with D-MPB (with daratumumab maintenance) in TI patients with NDMM. In both arms, bortezomib was subcutaneously administered twice weekly in the first course and once weekly in the second and subsequent courses. Patients in the daratumumab group had significantly longer PFS (primary endpoint) than those in the MPB group [18-month PFS: 71.6 vs. 50.2%; HR, 0.50; 95% confidence interval (CI), 0.38–0.65]. In the daratumumab group, a high percentage of patients achieved complete response (CR) or better (42.6 vs. 24.4%) and the overall response rate (ORR) (92.9 vs. 81.3%) was significantly high compared with the MPB group; the percentage of patients who were negative for minimal residual disease (MRD) (at a threshold of 1 tumor cell per 10^5 white blood cells) was also significantly higher in the daratumumab group than in the MPB group (22.3 vs. 6.2%). Patients in the daratumumab group had similar hematologic toxicity to those in the MPB group but had a high frequency of grade 3 or higher infections (23 vs. 15%), especially pneumonia (11 vs. 4%).

A long-term follow-up of the ALCYONE trial with a median observation period of 40.1 months reported a significantly longer OS (3-year OS: 78.0 vs. 67.9%; HR, 0.60; 95% CI, 0.46–0.80) among patients in the daratumumab group (22). However, notably, <10% of patients in the MPB arm received anti-CD38 antibody-containing second-line therapy, which may have worked in favor of the daratumumab group.

Daratumumab plus Ld. The MAIA trial (23) was a randomized controlled trial that compared Ld with D-Ld in TI patients with NDMM. Both regimens were administered as continuous therapy until the disease progressed. At a median follow-up of 28 months, patients in the D-Ld group had a significantly longer PFS (primary endpoint) than those in the Ld group (PFS at 30 months: 71 vs. 56%; HR, 0.56; 95% CI, 0.43–0.73). In the D-Ld group, the percentage of patients with CR or better (47.6 vs. 24.9%) and ORR (92.9 vs. 81.3%) was significantly higher than that of the Ld group. Further, the percentage of patients who were MRD-negative (at a threshold of 1 tumor cell per 10^5 white blood cells) was also significantly higher in the D-Ld group than in the Ld group (24.2 vs. 7.3%). Patients in the D-Ld group had a higher incidence of grade ≥ 3 neutropenia (50 vs. 35%), fatigue (8 vs. 4%) and pneumonia (14 vs. 8%) than those in the Ld group.

A long-term follow-up of the MAIA trial with a median observation period of 56.2 months showed that patients in the D-Ld group had a significantly better OS (HR, 0.68; 95% CI, 0.53–0.86) (24); however, since only 21% of patients in the Ld group received

Table 2. Recommended regimens for TI-NDMM in guidelines

Organization	JSH[a] (18)	ESMO (20)	NCCN[b] (19)
Published year	2020	2021	2021
Preferred regimen	D-MPB or D-Ld	D-MPB or D-Ld or BLd	BLd or D-Ld
Other recommended regimens	MPB or Ld or BLd or Bd or MPL or MP or CP or VAD or HDD	MPB or Ld	D-MPB

TI-NDMM, transplant-ineligible newly diagnosed MM; JSH, Japanese Society of Hematology; ESMO, European Society for Medical Oncology; NCCN; National Cancer Center Network; D-MPB, daratumumab plus elphalan, prednisone and bortezomib; D-Ld, daratumumab plus lenalidomide and dexamethasone; Bld, bortezomib, lenalidomide and dexamethasone; MPB, melphalan, prednisone, and bortezomib; Ld, lenalidomide and dexamethasone; M, melphalan; P, prednisolone; B, bortezomib; L, lenalidomide; d, dexamethasone; D, daratumumab; C, cyclophosphamide; V, vincristine; A, adriamycin; HDD, High-dose dexamethasone.

[a]Thalidomide-based regimens, which are not covered by the national health insurance in untreated patient settings, are not described. [b]Only regimens of category 1 are described.

anti-CD38 antibody-containing second-line therapy, this might have worked in favor of the D-Ld group.

Bortezomib, lenalidomide and dexamethasone. Another randomized controlled trial, the SWOG S07777, compared Ld with BLd in patients with NDMM without intention for immediate ASCT. BLd consisted of intravenous bortezomib (1.3 mg/m^2, day 1, 4, 8, and 11), lenalidomide (25 mg/day, days 1–14) and dexamethasone as induction therapy (every 3 weeks, up to eight cycles), followed by Ld until disease progression. The median observation period was 55 months, and the PFS (primary endpoint) and OS were significantly better with BLd than that observed with Ld (median PFS, 43 vs. 30 months, and median OS, 75 vs. 64 months, respectively). Patients in the BLd group frequently experienced severe neurotoxicity [grade 3 or higher peripheral neuropathy (PN): 33%; neuralgia: 12%], even after considering the intravenous administration of bortezomib. The proportion of patients who discontinued treatment owing to AEs was higher in the BLd group than in the Ld group (23 vs. 9.6%). In addition, less than half (43%) of patients in the BLd group were aged ≥65 years. Therefore, the BLd has been established as the standard therapy for TI patients with NDMM in the USA; however, it would not be suitable as a standard therapy for them in Japan (1).

The modified BLd, the so-called BLd lite, was developed to improve the tolerability of BLd in older patients. BLd lite consists of subcutaneous bortezomib (once weekly), lenalidomide (15 mg/day, days 1–21) plus dexamethasone as induction therapy (every 35 days for nine courses), followed by further reduction in the intensity of bortezomib and lenalidomide as consolidation therapy. After consolidation therapy, lenalidomide maintenance therapy was administered at the discretion of the treating physician. The efficacy and safety of BLd lite were evaluated in a phase II study in which 50 patients with a median age of 73 years (range: 65–91 years) were enrolled. The ORR (primary endpoint) was 86%, and the estimated median PFS was 35.1 months. Mild grade 1 (34%) or grade 2 (18%) PN occurred, and only one patient developed grade 3 PN (25). Although the efficacy and safety of BLd lite were better (as compared with BLd), the results should be interpreted with caution because they were from a single-arm phase II study that enrolled a small number of patients.

Continuous therapy. In the treatment strategy for MM, emerging evidence supports the benefit of continuous therapy for prolonging PFS without shortening the duration of response to subsequent therapy (26,27). Therefore, the abovementioned standard regimens (D-MPB, D-Ld and BLd) are continuously administered until disease progression.

Ixazomib monotherapy is an option for maintenance therapy. The significance of ixazomib maintenance therapy was evaluated in a phase III double-blind placebo-controlled study (TOURMALINE-MM4) (28). Patients with TI who achieved at least partial response as their best response to any standard of care induction therapy were recruited. The maximum course of maintenance therapy was 26 cycles. Patients who had been treated with a daratumumab-based induction regimen were not included because it was unavailable in clinical practice at that time. The ixazomib group showed a significantly longer PFS than the placebo group (median PFS since randomization, 17.4 vs. 9.4 months; HR, 0.66; 95% CI, 0.54–0.80) at the cost of increased gastrointestinal toxicity such as all grades of nausea (26.8 vs. 8.0%), vomiting (24.2 vs. 4.3%) and diarrhea (23.2 vs. 12.3%).

Areas where further investigation is required

Bortezomib-based regimen versus lenalidomide-based regimen

Prospective clinical trials to directly compare the MPB and Ld regimens are lacking; both of these regimens were previously the standard for Tl-NDMM treatment. Although daratumumab can be used combined with these regimens, there is no clear evidence suggesting whether D-MPB or D-Ld is the superior first-line therapy for Tl patients with NDMM.

From the comparison of results of the ALCYONE and MAIA trials, it can be concluded that D-Ld (median PFS, not reached; 95% CI, 54·8 months–not reached) yielded favorable outcomes as compared with the D-MPB (median PFS, 36.4 months; 95% CI, 32.1–45.9 months) (22,24); however, the results of two different trials cannot be simply compared. Regarding the MAIA trial, the median PFS (34 months) of the Ld group was far better than that of the Ld group in previous prospective trials (Table 3) (17,23,29). This might be partly explained by the increased clinician familiarity with the Ld therapy over time (24). However, as shown in Table 3, the median PFS of the Ld group in the TOURMALINE-MM2 trial (patient enrollment period between 2013 and 2015) was similar to that of the Ld group in the FIRST trial (patient enrollment period between 2008 and 2011). Therefore, other than familiarity with the Ld therapy, differences in background characteristics that were not fully captured may exist between clinical trials, which may affect the results. Although novel specific biomarkers, such as genomic or transcriptome alterations to predict the efficacy of bortezomib and lenalidomide, may help select better treatment agents, such information is currently insufficient.

How to utilize MRD testing

Improvements in MM therapy have led to more profound responses that are beyond the limit of detection for residual disease by

Table 3. Representative randomized phase III trial comparing Ld with other regimens

Trial name	FIRST (9,17)		TOURMALINE-MM2 (29)		MAIA (23,24)	
Period of patient enrollment	2008–11		2013–15		2015–18	
Design	Ld versus Ld18 versus MPT		Ld versus ILd		Ld versus D-Ld	
Regimen	Ld	Ld18	Ld	ILd	Ld	D-Ld
Median age, year (range)	73 (44–91)	73 (40–89)	74 (48–88)	73 (48–90)	74 (45–89)	73 (50–90)
>75 years, %	35	36	44	43	43.6	43.5
ISS III, %	40	40	16.7	16	29.8	29.1
PS 2, %	22	21	14.4	16.5	16	17.1
With high-risk CA, %	17	20	17.8	17.1	13.6	15
Treatment outcomes						
Median PFS, months	26	21	21.8	35.3	34.4	NR
CR rate, %	22	20	14.1	25.6	30	51
Overall response rate, %	81	79	79.7	82.1	81.6	92.9

Ld, lenalidomide and dexamethasone; Ld18, Ld up to 18 cycles; MPT, melphalan, prednisolone and thalidomide; ILd, ixazomib plus Ld; CA, cytogenetic abnormality; PFS, progression-free survival; NR, not reached; CR, complete response.

monoclonal proteins in the serum and urine and conventional bone marrow examination. Therefore, more sensitive techniques for assessing residual disease, including the next-generation flow cytometry and NGS, have been developed (30). In Japan, next-generation flow cytometry is available in clinical practice (31).

The significance of MRD status as a prognostic factor has also been established. In a recent meta-analysis, the achievement of undetectable MRD (threshold of MRD sensitivity was 10^{-4}, 10^{-5} or 10^{-6}) improved PFS (HR, 0.33) and OS (HR, 0.45) in comparison with the presence of MRD (32). Importantly, the outcomes of patients who achieved CR or better can be stratified by the MRD status; compared with positive MRD, undetectable MRD was associated with favorable PFS (HR, 0.38) (32).

However, modifying treatment based on MRD status is presently not recommended in clinical practice. Clinical trials to evaluate MRD-guided treatment strategies only started mainly targeting patients who had received ASCT. For example, the Southwest Oncology Group is conducting a phase III study to evaluate the impact of MRD negativity on further continuing the treatment. Patients who achieved MRD negativity by NGS after 2 years of maintenance therapy (lenalidomide with or without daratumumab) were randomized to continue or discontinue maintenance therapy (NCT04071457). Meanwhile, findings obtained from these trials will be useful when considering the MRD-guided treatment strategy for TI patients.

Notably, there are certain issues in MRD testing which should be considered for the further development of MRD-guided treatment strategy. For example, the bone marrow sample for MRD assessment is probably not associated with the entire tumor burden, especially in the case of macrofocal or extramedullary disease. Positron emission tomography may compensate for the limitations in assessing MRD in bone marrow samples (33). In addition, if an MRD-guided treatment strategy is established in a clinical study, the same MRD testing should be used to extrapolate the results. Therefore, standardization of MRD testing is an important issue.

Treatment strategy for frail patients

The clinical trials described above have established the standard therapies for older patients with NDMM. Applicability of the results of these trials to frail patients was evaluated in a supplemental study of the ALCYONE and MAIA trials. In frail patients defined by the simplified frailty score (10), the addition of daratumumab resulted in improved PFS at the cost of increased AEs, such as neutropenia and infections, which were generally well tolerated (the proportion of frail patients who discontinued the study treatment due to AEs were smaller in the daratumumab arm than in the standard arm in both studies) (34,35). However, it should be noted that the inclusion and exclusion criteria for the studies may limit the generalizability of these results to more frail patients encountered in clinical practice. In addition, a simplified frailty score may not be specific enough to detect frail patients because approximately half of the patients (45 and 46%) enrolled in ALCYONE and MAIA trials, respectively, were defined as frail (34,35).

Several clinical trials to develop optimal treatment regimens for frail patients have been conducted. For example, HOVON 143 was a phase II trial that evaluated the efficacy and safety of ixazomib, daratumumab and dexamethasone, targeting frail patients according to the IMWG frailty score (36). The primary endpoint was the ORR. In this study, 65 patients were enrolled, and the ORR (78%; 95% CI, 0.73–0.82) was better than the prespecified threshold of 65%. After a median follow-up of 22.9 months, the median PFS and OS were 13.8 and 12 months, respectively. However, in 51% of the patients, induction therapy had to be discontinued prematurely because of toxicity or early death as the major reasons. An additional 12 patients discontinued ixazomib because of PN in 10 out of 12 patients even with low-grade severity (grade 1 or 2 in seven patients) (36). Therefore, it is important to consider that even low-grade AEs can affect treatment adherence in frail patients. Interestingly, patients who were considered frail (based only on age) showed better PFS (median, 21.6 months) and OS (12 months, 92%) than patients who were considered frail based on other frailty parameters (36). Although this subgroup analysis involved a small number of patients, these results may suggest that there is heterogeneity even among frail patients, as defined by the IMWG frailty score.

Although both IMWG and simplified frailty scores, which are popular frailty indexes, are validated, further investigations are warranted to develop more specific frailty scores to select frail patients, which would help establish more optimal treatment strategies.

The Japan Clinical Oncology Group trial for MM

JCOG1105 (jRCTs031180097). The lymphoma study group (LSG) of the Japan Clinical Oncology Group (JCOG) (JCOG-LSG) conducted a randomized phase II trial (JCOG1105) comparing two modified

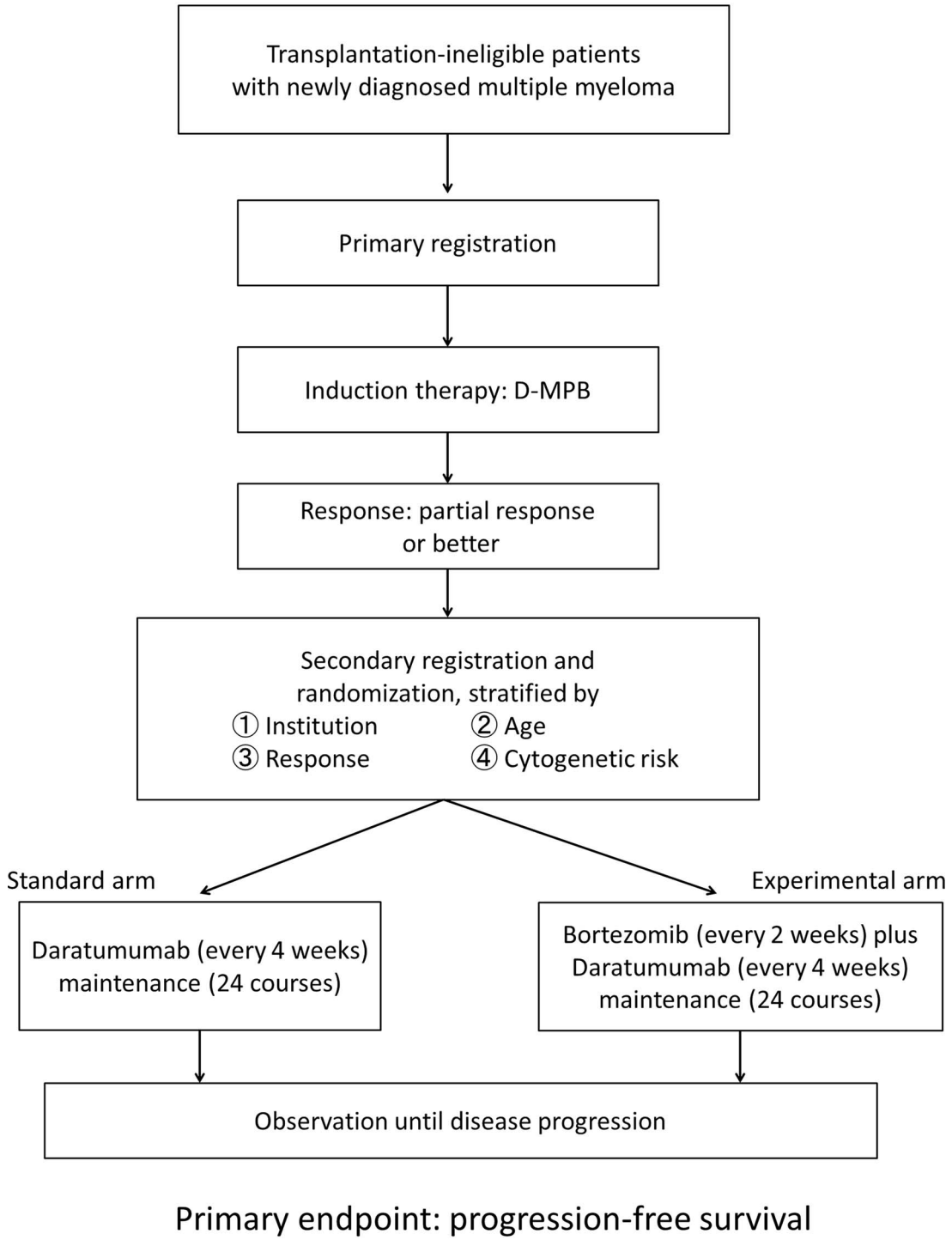

Figure 1. Study schema of JCOG1911. Patients who respond to daratumumab, melphalan, prednisone and bortezomib (D-MPB) induction therapy will be randomized to receive daratumumab or bortezomib plus daratumumab maintenance therapy. The primary endpoint is progression-free survival.

MPB regimens in TI patients with NDMM (37). Patients were randomized to arm A (twice-weekly bortezomib in a 6-week cycle followed by eight 5-week cycles of four times once-weekly bortezomib with melphalan and prednisone on days 1–4) or arm B (nine 4-week cycles of three times once-weekly bortezomib with melphalan and prednisolone on days 1–4). The primary endpoint was the CR rate (%CR). No maintenance therapy was planned for either arm. In total, 91 patients were enrolled; patients in arm A showed better %CR (18.6 vs. 6.7%) and median PFS (2.5 years vs. 1.4 years; HR, 1.93; 95% CI, 1.09-3.42) than those in arm B. Although there was a slight increase in the frequency of AEs in arm A, they were generally well tolerated. The result of JCOG1105 proposed that the twice-weekly dosing of bortezomib in the first cycle, along with a higher dose of melphalan and higher cumulative

Table 4. Ongoing Phase III trials for TI-NDMM patients with patients being currently recruited or who have been recruited

Treatment	Eligible age (years)	Inclusion/exclusion criteria regarding frailty	Primary endpoint	Identifier
Isa + BLd versus Isa+Ld[a]	65–79	Included: non-frail patients	MRD negative rate	NCT04751877
Dara+BLd versus BLd[b]	≥18	Excluded: frail patients according to IMWG frailty score (8)	MRD negative rate	NCT03652064
BLd followed by Cilta-cel versus BLd followed by Ld[b]	≥18	Excluded: frail patients according to IMWG frailty score (8)	PFS	NCT04923893
CLd versus Ld[a]	≥65	Included: fit or intermediate-fit patients according to IMWG frailty score (8)	MRD negative rate and PFS	NCT04096066
MPB followed by Ld versus CLd versus Dara-CLd[a]	65–80	Included: fit patients by GAH scale (43)	CR rate	NCT03742297
ILd versus dose-modified ILd according to the MRP (11)[a]	≥18	NA	Early treatment-cessation rate	NCT03720041
Isa + BLd versus BLd	18–80	NA	PFS	NCT03319667

Isa, isatuximab; MRD, minimal residual disease; Dara, daratumumab; Cilta-cel, ciltacabtagene autoleucel; C, carfilzomib; I, ixazomib; GAH, geriatric assessment in hematology; NA, not applicable.
[a]The trial was not performed in Japan. [b]Patients eligible for hematopoietic stem cell transplant, which was not planned as initial therapy, are also included

dose of both bortezomib and melphalan, influences the efficacy of the modified MPB regimen as an induction treatment in TI patients with NDMM.

JCOG1911 (jRCTs031200320). In JCOG1105, the optimal MPB regimen was determined as arm A. Based on the results of the JCOG1105 and ALCYONE trials, D-MPB was considered the standard therapy for TI-NDMM in the JCOG-LSG. JCOG1911, a randomized phase III study, was designed to compare bortezomib plus daratumumab with daratumumab as maintenance therapy after D-MPB induction. As for maintenance therapy in the experimental arm, bortezomib was administered on days 1 and 15 and was combined with daratumumab every 4 weeks. The duration of maintenance therapy was fixed at up to 24 cycles (~2 years) in both arms. The primary endpoint was PFS, and schematics of JCOG1911 are shown in Fig. 1.

Regarding the background of JCOG1911, in the ALCYONE trial, the PFS in the daratumumab group declined more sharply during the administration of daratumumab maintenance therapy than in the induction phase. Therefore, reinforcement of daratumumab maintenance therapy is needed to improve the treatment outcomes of patients receiving D-MPB. The efficacy and tolerability of bortezomib are well confirmed at the start of maintenance therapy in patients administered D-MPB. This is one of the rationales bortezomib is being considered the most promising adjunct therapy to daratumumab maintenance therapy. In addition, it is expected that the poor prognosis of high-risk CAs would be improved by maintenance therapy, including proteasome inhibitors.

Patients are currently being recruited for this study. As an exploratory biomarker study of JCOG1911, NGS-based analyses of genetic alterations in tumor samples obtained at initial diagnosis and during disease progression have been planned. The genetic alterations associated with poor prognosis in patients uniformly treated with D-MPB and resistance to D-MPB will be evaluated. Moreover, the IMWG frailty score was prospectively evaluated at study enrollment in JCOG1911 to reveal the significance of frailty status, defined by the IMWG frailty score, in patients who were uniformly treated with D-MPB.

Future direction

Combination therapies incorporating daratumumab have improved the treatment outcomes of all TI-NDMM patients with good safety profiles. By contrast, in recent years, several clinical trials, including TI-NDMM patients, focused on stratifying treatments by frailty; a more intensive induction regimen for fit or non-frail patients is being evaluated (Table 4). Furthermore, immunotherapies targeting a novel tumor-specific antigen have been vigorously tested in relapsed or refractory MM patients. B-cell mature antigen (BCMA) is one of the most promising targets, and antibody–drug conjugate (38), bispecific antibody (39), bispecific T-cell engager (40) and chimeric antigen T-cells (CAR T-cells) (41,42) which target BCMA showed high clinical efficacy. The usefulness of such novel immunotherapies will certainly be explored as earlier lines of therapy; however, information on their efficacy and safety is inadequate and should, therefore, be evaluated carefully. In fact, a phase III clinical trial on non-frail TI-NDMM patients (NCT 04923893) is currently being conducted to evaluate the efficacy of consolidative BCMA CAR T-cell therapy after BLd induction. Considering all these details, future treatments for TI-NDMM patients are expected to be stratified by the frailty status. Fit older adults will receive intensive regimens, such as quadruple regimens (anti-CD38 antibody, proteasome inhibitor, immunomodulatory drug and steroid) or regimens incorporating novel immunotherapy. Consequently, older adults will achieve MRD negativity more frequently, which drives the development of MRD-guided treatment strategies. On the contrary, frail patients should also benefit from treatment advances; the usefulness of novel immunotherapies for frail patients requires evaluation in future clinical trials adopting appropriate patient selection criteria.

Conclusion

Large-scale randomized clinical trials have shown the effectiveness of several novel treatment regimens in older adults with MM. Although the prognosis of patients with MM has dramatically improved, this is only limited to those who can tolerate them. Supplemental and integrated analyses of these trials identified several patient- and disease-based prognostic factors, such as R-ISS, high-risk CAs, frailty

and MRD. The utilization of these factors to determine treatment strategies is an urgent issue. For older adults, frailty can be the most important factor guiding the optimal treatment plan because the demerits of intensifying treatments, such as increased toxicity, sometimes outweigh the merits, especially in frail patients. Therefore, while it is important to continue developing more effective new treatments for older adults through clinical trials, further investigation is warranted to develop an optimal treatment strategy for frail patients as well as more specific tools for determining frailty.

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Conflict of interest

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