Treatment Patterns in Newly Diagnosed Multiple Myeloma Patients in Japan Using A Large-scale Claims Database: Retrospective Cohort Study

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〈Abstract〉

Objective: To describe the treatment patterns and time to next treatment (TTNT) in newly diagnosed multiple myeloma patients (MM) using a large-scale claims database in Japan.

Design: Cohort study

Methods: The patients with newly diagnosed MM from 2008 to 2015 were classified into two groups: age <65 years, and age ≥65 years. Specific regimens and general regimens were identified with a complex algorithm considering interval of no therapy, additional and discontinued agents. Correspondingly, TTNT between the first- and second-line were measured among non-transplant patients with Kaplan-Meier method.

Results: A total of 425 patients were eligible to participate in the analysis. The most common regimen for the treatment of MM was bortezomib-based regimens (52.9% in the first-line, 28.2% in later lines), followed by melphalan-prednisolone (27.1% in the first-line, 12.9% in later lines) and lenalidomide-based regimens (4.7% in the first-line, 26.1% in later lines). TTNT between the first- and second-line was 11.4 months and was seen to vary greatly with each regimen. A statistically longer TTNT was observed in subgroups of patients aged 65 years or over compared with patients aged younger than 65 years, but no statistical difference was found between conventional therapy and novel therapy.

Conclusion: Based on the data from the study, patients with MM were commonly treated with novel agent-based regimens, especially bortezomib-based regimens. Between the first- and second-line therapies a relatively short TTNT was observed, indicating that therapies in clinical practice poorly complied with treatment guidelines.

Keywords: multiple myeloma, drug therapy, administrative claims, healthcare, retrospective studies, Japan

Introduction

Multiple myeloma (MM) is a malignant neoplasm caused by plasma cell dyscrasia. In 2009, the age-standardized rates of MM for males and females were 2.9 per 100,000 persons and 2.1 per 100,000 persons, respectively, in Japan, and 2.0 and 1.4 per 100,000 persons worldwide.1)
The median age of Japanese patients when diagnosed with MM was 66 years, and the incidence and mortality increased with age.\textsuperscript{1}

Over the past decade, novel agents for the treatment of MM in Japan included bortezomib (BOR, approved in 2006), thalidomide (THAL, approved in 2008), lenalidomide (LEN, approved in 2010), and pomalidomide (POM, approved in 2014), all of which have achieved a striking improvement in patient outcomes.\textsuperscript{2–5} More importantly, an extension in overall survival was observed in Japanese patients after the introduction of novel agents.\textsuperscript{6}

NCCN and ESMO clinical practice guidelines have recommended BOR+cyclophosphamide (CPM) + dexamethasone (DEX), BOR+doxorubicin (DXR) + DEX, and BOR+LEN+DEX for transplant candidates, and BOR+LEN+DEX and LEN+low-dose DEX for non-transplant candidates as primary therapies. Autologous transplantation was recommended proceeding straight after induction therapy to high-dose therapy for transplant candidates.\textsuperscript{7,8} Historically, transplant was not considered as an option for patients older than 65 years, correspondingly in clinical practice, patients who received stem cell transplantation (SCT) were significantly more likely to be under 65 years as initiation therapy than those who did not.\textsuperscript{9}

In Japan, a retrospective cohort study reported that the most common regimens among relapsed/refractory MM patients were BOR ± DEX, melphalan (MEL) + prednisolone (PSL), and LEN ± DEX between 2008 and 2016.\textsuperscript{10} MM was managed by successive each line of therapies (LT), which resulted in shorter response duration over prior LT.\textsuperscript{11} However, prior studies did not address the treatment patterns and clinical outcomes among newly diagnosed MM patients in Japan. Therefore, we investigated the treatment patterns for MM patients with respect to age and transplantation using a large-scale claims database in Japan.

Patients and Methods

Data source

We conducted a retrospective cohort study using anonymous claims data provided by Medical Data Vision Co., Ltd. (MDV : Tokyo, Japan),\textsuperscript{12} an organization that has collected data since April 2008. The MDV database contains information for 11.66 million inpatients and outpatients (over 9% of the Japanese population) from 208 hospitals in Japan as of September 2015. The database comprises information such as anonymized patient identifiers, age, sex, diagnosis, laboratory test, procedure, surgery, prescription, and discharge summary.

The protocol of this study was approved by the Committee of Medical Ethics, Graduate School of Medicine, Kyoto University (protocol number : R0193). Informed consent was waived since the database protects patient anonymity.

Patients

We identified patients with newly diagnosed MM (ICD-10 code, C900) aged 18 years or older between April 1, 2008 and September 30, 2015. Newly diagnosed MM was defined as 1) the first diagnosis date later than April 1, 2008 and later than the date of first medical record for the patient in MDV database, whichever came later; or 2) at least one medical record of suspected MM before diagnosis. Patients were excluded if only hospitalization records exist since from date for case of hospitalization in MDV database could not be identified as first diagnosis date. We excluded information from patients who only had a suspected diagnosis of MM, did not receive any medication for MM therapy, died within one month after diagnosis with MM, or could only be followed for less than one month. The date of initial MM diagnosis was defined as an index date and patients were followed from this date to the cause of death, completion of the study (September 30, 2015), or until loss before the follow-up period, whichever came first.

All patients were classified into two groups according to their age and corresponding treat-
ment strategies: age <65 years (younger group), and age ≥65 years (elderly group).

Demographic characteristics were primarily measured on the index date. We measured all the diseases within one year before the index date and calculated Charlson Comorbidity Index (CCI) score\(^{13}\) for comorbidity evaluation. Laboratory test results were extracted within one month of the index date.

**Treatment patterns**

We identified the prescription of agents for MM therapy, novel agents (BOR, LEN, THAL, and POM), and conventional agents (MEL, vincristine (VCR), CPM, DXR, DEX and PSL). The algorithm to determine treatment lines and specific regimens was based on three steps (Figure 1): 1) A time gap without therapy for MM over 28 days was considered as start of the subsequent treatment line, but if the 2 consecutive regimens were the same, then they were regarded as in the same treatment line.\(^{14}\) 2) An agent for MM therapy initially prescribed over 28 days later than the start date of previous agent was also defined as start of the sequential treatment line.\(^{15,16}\) 3) Discontinuation of a single agent from a combination regimen was not considered as a change of treatment line, which may due to an adverse event or health condition.\(^{17}\) After identifying the crude treatment lines, we excluded regimens with single PSL or single low-dose DEX (<16.5 mg per day) as they are generally prescribed for other diseases. We then repeated the above algorithm to identify the final treatment lines and specific regimens.

If the sequential specific regimens contained the same main agent, we categorized them as a general regimen such as BOR-based regimens, LEN-based regimens, THAL-based regimens, POM-based regimens, and melphalan-prednisolone (MP)-like regimens. If two or more novel agents were prescribed in a specific regimen, this was defined as a combined regimen using novel agents. With the exception of the above-mentioned general regimens, we also identified

**Step 1.** A time gap without therapy for MM over 28 days was considered as start of the subsequent treatment line, but if the 2 consecutive regimens were the same, then they were regarded as in the same treatment line.

\[
\begin{align*}
A & \rightarrow \text{>28 days} \rightarrow B \\
1\text{st regimen} : A \\
2\text{nd regimen} : B
\end{align*}
\]

**Step 2.** An agent for MM therapy initially prescribed over 28 days later than the start date of previous agent was also defined as start of the sequential treatment line.

\[
\begin{align*}
A & \rightarrow \text{<28 days} \rightarrow B \\
1\text{st regimen} : A + B \\
2\text{nd regimen} : A + B + C
\end{align*}
\]

**Step 3.** Discontinuation of a single agent from a combination regimen was not considered as a change of treatment line, which may due to an adverse event or health condition.

\[
\begin{align*}
A & \rightarrow \text{>28 days} \\
1\text{st regimen} : A + B \\
2\text{nd regimen} : C
\end{align*}
\]

**Figure 1** Algorithm created to identify treatment patterns

VCR-DXR-DEX (VAD), and DEX (≥16.5 mg per day), and "Other regimens" represented regimens that have not been mentioned above.

**Time to next treatment between the first- and second-line therapies**

We used time to next treatment (TTNT) as the clinical outcome of the study. TTNT between the first- and second-line therapies was defined as the time from the start of initial therapy to the start of the subsequent line of therapy. The patients who accepted SCT were excluded due to the potentially short and fixed period of the induction therapy.
We evaluated the differences of TTNT among subgroups by age and therapy, age <65 years versus age ≥65 years, and novel regimens versus conventional regimens, respectively. During the first treatment line, patients who died, or lost follow-up, were censored at the date of last medical record.

**Statistical analysis**

We described the study variables including patient characteristics and treatment patterns. Continuous measurements were summarized as the mean and standard deviation or as the median and interquartile range; counts and percentages were calculated for categorical variables. TTNT was described with the Kaplan-Meier method and was compared between younger and elder patients, and patients receiving novel regimens versus conventional regimens, with the log-rank test. A two-sided α level of 0.05 was considered statistically significant. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

**Results**

**Patients**

A total of 425 newly diagnosed MM patients were eligible for the analysis (Figure 2). Of these patients, 118 (27.8%) were younger patients (age <65 years), and 307 (72.2%) were elderly patients (age ≥65 years) (Table 1). Overall, the mean age at diagnosis was 70 years; besides, the mean age per group was 55 and 75 years in the younger group and elderly group, respectively. Overall, 56.5% of patients were males and they accounted for 60.2% patients in the younger group. The most common comorbidities among patients were essential hypertension (31.8%), constipation (22.6%), and lower back pain (16.7%). The most frequent CCI score was between 1–2 points in all three groups (41.9%). Laboratory tests showed that 48.1% of patients had high albumin, 14.6% had high creatinine, 47.9% had low hemoglobin, 24.4% had high albumin-corrected calcium levels and 11% had abnormal LDH at diagnosis. Since the MDV database collected patients’ data mainly from 2010, less data (6.4%) were obtained for patients who were diagnosed in 2008 and 2009.

**Treatment patterns**

The most common general regimen was the BOR-based regimen (38.4%), and BOR+DEX was the most common specific regimen. MP-like regimens were the second most commonly prescribed regimens (19.0%), followed by LEN-based regimens (14.6%), other regimens (7.6%), THAL-based regimens (5.7%), SCT (4.6%), DEX (4.0%), combined regimen of novel agents (3.8%), VAD (1.2%), and POM-based regimens (1.0%). With the exception of MP-like regimens and THAL-based regimens, DEX was the most frequently used adjuvant combined with a novel or conventional agent. In the combined regimen of novel agents, BOR+LEN+DEX was most commonly prescribed (Figure 3).

BOR-based regimens and BOR+DEX were optimal in both groups. However, MP-like regimens were more frequently used than LEN-based regimens in the elderly group. The proportions of the remaining regimens appeared to be similar between the two groups.

Among all the MM patients, 78.4% used any
novel agent-based regimens at least once. BOR-based regimens were used at least once by 65.4% of all patients, 87.3% of younger patients, and 57% of elder patients. MP-like regimens were mainly used in the elderly group (43.3%). LEN-based regimens were the third most common regimen and its use was higher in the younger group (32.2%) than the elder group.
Figure 3 Frequency of treatment regimens in (a) all patients; (b) younger group; (c) elderly group.

Abbreviations:
BOR, bortezomib; MP, melphalan-prednisone; LEN, lenalidomide; THAL, thalidomide; SCT, stem cell transplantation; DEX, dexamethasone; VAD, vincristine-doxorubicin-dexamethasone; POM, pomalidomide; CPM-i, cyclophosphamide injection; MPT, MP+THAL; MEL-i, melphalan injection.
TTNT between the first- and second-line

The median TTNT between the first- and second-line was 11.4 months among patients in the non-transplant group. This value varied greatly for each general regimen. TTNT of THAL-based regimens (42.6 months), LEN-based regimens (37.7 months), and MP-like regimens (13.2 months) was longer than that of other regimens, whereas, TTNT of BOR-based regimens (9.9 months) was relatively short. The elderly patients showed a slightly longer TTNT than the younger patients (12.0 months vs. 7.8 months) (Table 2).

A statistical difference of TTNT was found between patients age <65 years and age ≥65 years (log-rank p-value 0.02). However, patients receiving novel regimens and conventional regimens were observed no statistical difference (log-rank p-value 0.22). (Figure 4).

### Discussion

This real-world data based retrospective study spanning from 2008 to 2015 showed the increase in availability of novel agents over recent years. Novel agent-based regimens were commonly used as treatment for MM among younger patients (<65 years), and elderly patients (≥65 years): however, utilization of MP-like regimens accounted for a noticeable proportion among elderly patients. TTNT between the first- and second-line therapies among non-transplant patients was relatively short, and was found to be significantly longer in elder patients.

### Treatment patterns

The most common treatment regimens were BOR-based regimens, MP-like regimens, and LEN-based regimens, which was consistent with a previous study on relapsed/refractory MM patients in Japan. It was noteworthy that the conventional regimen, MP-like regimens, remained highly preferred by the elderly patients in the current study. This is similar among patients aged ≥75 years in the US before 2008. In recent years, the utilization of MP-like regimens has declined in the US (6.8%) and France (9.4%), and the novel BOR-based regimens, LEN-based regimens, and BOR + LEN/THAL have become the most commonly used regimens in the US.

Although triplet regimens were more recommended than double regimens for frontline therapy based on their superior clinical outcomes, we found that only a few specific regimens contained a triplet of drugs. A notable number of elderly patients treated with conventional chemotherapies and a clear majority of double regimens among all patient groups suggest an association with

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**Table 2** Time to next treatment between the first- and second-line therapies among non-transplant patients

| General regimens       | All patients | Age<65 years | Age≥65 years | Log-rank p value |
|------------------------|--------------|--------------|--------------|------------------|
|                        | n Median (m) | n Median (m) | n Median (m) |                  |
|                        | IQR (m)      | IQR (m)      | IQR (m)      |                  |
| All                    | 386 11.4 [3.4-34.5] | 86 7.8 [2.6-21.7] | 300 12.4 [4.2-37.7] | 0.1424          |
| BOR-based              | 194 9.9 [2.7-34.5] | 65 5.8 [2.6-N/E] | 129 10.2 [4.1-23.7] | 0.8809          |
| MP-like                | 114 13.2 [5.5-25.7] | 3 6.9 [5.5-8.3] | 111 14 [5.4-25.7] | 0.1958          |
| LEN-based              | 20 37.7 [20.9-N/E] | 4 21.7 [21.7-21.7] | 16 37.7 [20.9-N/E] | 0.8507          |
| Other regimens         | 15 6.1 [1.5-15.1] | 4 15.1 [7.6-15.1] | 11 6.1 [1.5-N/E] | 0.7132          |
| THAL-based             | 15 42.6 [23.9-45.7] | 1 14 [14.0-14.0] | 14 42.6 [28.6-45.7] | 0.0488          |
| DEX                    | 20 0.7 [0.5-8.7] | 4 0.6 [0.5-N/E] | 16 1.3 [0.5-8.7] | 0.7870          |
| novel combined         | 4 6.8 [4.5-N/E] | 2 N/E [4.5-N/E] | 2 6.8 [6.8-6.8] | 0.8084          |
| VAD                    | 4 1.3 [1.1-9.4] | 3 5.4 [1.3-9.4] | 1 1.1 [1.1-1.1] | 0.1573          |

Abbreviations: BOR, bortezomib; MP, melphalan-prednisone; LEN, lenalidomide; THAL, thalidomide; DEX, dexamethasone; VAD, vincristine-doxorubicin-dexamethasone; IQR, interquartile range; N/E, not estimable.
conservative options by physicians. The delayed approval of novel agents for MM therapy in Japan compared to the US and Europe may also impact this trend.

**TTNT between the first- and second-line therapies**

In the current study, we found that the TTNT of most regimens was shorter than that reported in clinical trial\(^{(25) - (28)}\) and other studies have reported a similar finding.\(^{(10),(19)}\) The estimates of TTNT from the real-world may not be comparable to those from the clinical trials as TTNT was found to be affected by various factors (e.g., comorbidities, disease progression, and adverse events) in our study. LEN-based regimens indicated a significantly longer TTNT than BOR-based regimens in the current study, which was also found in a previous study that used the US claims database.\(^{(29)}\)

It was important to note that the elder patients suggested a markedly longer TTNT than the younger patients in our first finding. Further studies are required to confirm this possibility; however, this may have been a result of adequate tolerance of MEL and LEN, which preferred by elder patients.\(^{(30)}\) We didn’t see significant difference of TTNT between novel therapy and conventional therapy for the frontline among non-SCT patients. Results from a study in Latin America also showed those who received BOR-based therapy had non-significantly better pro-

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![Figure 4](image-url)  
Figure 4 Time to next treatment between the first- and second-line among patients  
(a) age <65 years vs. age ≥65 years; (b) received conventional therapy vs. novel therapy
gression free survival than those who received conventional chemotherapy.\textsuperscript{31}

\textbf{Limitations}

There were several limitations in this study. First, the definition of newly diagnosed MM was mainly determined by from date and suspicious MM record which were not validated in MDV database. Besides, we didn’t take the strategy of washout period, which were due to the long progression free survival of MM (median: 21 months for non-SCT and 42 months for SCT) and the use of maintenance therapy increasingly during the progression free interval.\textsuperscript{32} Thus, we might include the patients with relapsed MM in case of incorrect information of from date or suspicious MM record. So further validation study would be necessary for a better identification of newly diagnosed patients. Second, the validity of algorithms to identify treatment lines and regimes was not established, potentially resulting in misclassification. But comparing with the published papers regarding algorithms used for identifying treatment patterns for MM, our algorithms considered more details and more scientific. In addition, maintenance therapy may potentially be identified as a second-line therapy based on this algorithm, which may result in a shorter TTNT, but treatment patterns still kept the reliability. Third, follow-up periods, TTNT, and number of patients in the second- and later lines might have been underestimated because follow-up may have been lost due to a hospital change, as well as a large proportion of patients had no therapy. This issue existed in all claims database if people didn’t have their own identification number. As switching to a subsequent treatment line may be caused by various reasons (e.g., stable disease, disease progression, adverse events, or economic reasons), we were unable to discover the cause of switching to the subsequent line using this database research, further limiting our study.

\textbf{Conclusion}

In conclusion, patients with MM were commonly treated with novel agent-based regimens, especially BOR-based regimens, although elderly patients preferred MP-like regimens. Between the first- and second-line therapies a relatively short TTNT was observed, indicating that therapies in clinical practice poorly complied with treatment guidelines.

\textbf{Author contributions}

JG, ST, SY, KK designed and performed the research. JG, ST analyzed the data, JG, ST, IS wrote the manuscript. All authors read and approved the manuscript.

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\textbf{Conflicts of interest}

KK received honoraria from Shin Nippon Biomedical Laboratories, Ltd.; research funds from Olympus Corporation, Sumitomo Dainippon Pharma Co., Ltd., Bayer Yakuhin Ltd., Stella Pharma Corporation, Novartis Pharma K.K., CMIC Co., Ltd., Amgen Astellas BioPharma K.K., Suntory Beverage & Food Ltd., and Medical Platform Co., Ltd.; and holds stocks in School Health Record Center Co., Ltd. and Real World Data, Co., Ltd. There are no patent products under development or marketed products to declare that are relevant to those companies. Other authors: None declared.

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