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Letter to the Editor

Treatment of Multiple Myeloma in Akita: Features and Outcomes in the Era of Novel Agents

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TO THE EDITOR

Multiple myeloma (MM) manifests as indolent neoplasms composed of plasma cells, but has a lethal clinical course and responds poorly to therapy.[1] In Japan, MM affects 2.4 men and 1.7 women per 100,000 individuals each year. The median age of onset is 66 years in Japan.[2] In recent years, MM treatments have changed dramatically, and new agents (such as proteasome inhibitors and immunomodulatory drugs) have been found to provide prolonged survival for patients with MM.[3,4] In a large retrospective study conducted at the Mayo Clinic, patients who were treated with the novel agents were observed to have longer survival following their initial diagnoses, as well as after relapse.[3] Several clinical trials have reported that the novel agents can achieve complete response, which is associated with improved progression-free and overall survival. Bortezomib is superior to high-dose dexamethasone for the treatment of patients with MM who have experienced a relapse after 1 to 3 previous therapies. In comparison with high-dose dexamethasone, the hazard ratio (HR) for death with bortezomib was 0.57 ($P = 0.001$).[5] Two pivotal, phase III, randomized and placebo-controlled registration trials (MM-009 and MM-010) showed that lenalidomide plus dexamethasone was a more effective treatment regimen than placebo plus dexamethasone for patients with relapsed or refractory MM.[6,7] Overall survival was significantly improved in the lenalidomide group (HR for death, 0.66; $P = 0.03$).[6] The phase III VISTA (Velcade® as Initial Standard Therapy in Multiple Myeloma) randomized clinical trial indicated that bortezomib plus melphalan and prednisone significantly prolongs overall survival in comparison with melphalan plus prednisone (HR, 0.653; $P < 0.001$).[8,9] This trial included a median follow-up of 36.7 months. Moreover, in the Front-Line Investigation of Revlimid®/Dexamethasone vs. Standard Thalidomide (FIRST) randomized clinical trial, a doublet regimen of continuous oral lenalidomide in combination with low-dose dexamethasone was demonstrated to confer a statistically significant improvement in progression-free survival as a primary endpoint, in comparison with a comparator triplet regimen of melphalan, prednisone, and thalidomide.[10] The novel agents bortezomib and lenalidomide have been approved for MM treatment in Japan; however, limited data are available on the outcomes of treatment with these novel agents in clinical practice. Such data are important because treatment outcomes may differ substantially outside the highly regulated settings of randomized controlled trials. Shimizu *et al*.[11] investigated the survival of 1,383 Japanese patients with MM who were treated before the

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novel agents were introduced. Median survival was reported to be 3.3 years among 1,162 patients treated with chemotherapy, and 4.4 years among 113 patients treated with a high-dose therapy followed by stem cell transplantation.[11] On the other hand, on the basis of data from a single institution, Chou[12] found several improvements in MM treatment with the novel agents. To investigate the clinical outcomes of MM in the era of new agents, we conducted a retrospective review of patients in Akita prefecture who received treatment for MM in general clinical practice.

A total of 205 Japanese patients with MM (106 men and 99 women) were newly diagnosed and treated in Akita prefecture between July 2006 and June 2013. The main clinical characteristics of these 205 patients with MM are presented in Table 1. The median age at diagnosis was 72 years (range, 33-93 years). Seventy-one patients (50.7%) were alive at last follow-up. The median follow-up period for these patients was 574 days (7-2,401 days) after diagnosis. One hundred and twenty-seven patients (62.0%) were treated with the novel agents during their clinical courses. Sixty-three patients (31.7%) received the novel agents during induction therapy, which included bortezomib-based regimens (n = 34), lenalidomide-based regimens (n = 25), and thalidomide-based regimens (n = 4). Twenty-one patients (10.2%) underwent autologous stem cell transplantation. There were several significant differences between the new-agent group and the conventional chemotherapy group. Patients in the new-agent group were younger than those in the conventional therapy group ($P < 0.0001$) and hemoglobin levels were higher in the new-agent group than in the conventional chemotherapy group ($P = 0.0044$).

Fig. 1 presents the various symptoms that triggered diagnosis at the onset of MM. Back pain and lumbago were frequently observed in MM patients. Half of the MM patients had visited a hospital as a result of orthopedic problems, including back pain or lumbago, bone pain, coxalgia, and thoracodynia. On the other hand, 20% of MM patients had visited a hospital for nonspecific symptoms (e.g., fever, fatigue, edema, or anorexia). The remaining MM patients had not experienced subjective symptoms and were diagnosed on the basis of abnormal laboratory findings (e.g., monoclonal gammopathy, proteinuria, or anemia) that were revealed by medical examinations. According to the myeloma-related organ dysfunction criteria (CRAB),[13] hypercalcemia (adjusted serum calcium level > 11.5 mg/dL) was observed in 31.7% of patients, renal insufficiency (serum creatinine level > 2 mg/

Table 1. Patient characteristics

Clinical data	Total (n = 205)	New agents (n = 127)	Conventional (n = 78)	*P*-value	Orthopedic group (n = 88)	Non-orthopedic group (n = 117)	*P*-value
Median age, years (range)	72 (33-93)	68.5 (33-88)	78.5 (49-93)	< 0.0001	70.0 (33-90)	74.0 (48-93)	0.0237
Gender, Men/women (%)	106/99 (52/48)	73/54 (58/42)	33/45 (42/58)	0.0348	45/43 (51/49)	61/56 (52/48)	0.8872
Type of myeloma, n (%)							
IgG	125 (61.0)	76 (59.8)	49 (62.8)	0.5066	53 (60.2)	72 (61.5)	0.4268
IgA	58 (28.3)	37 (29.1)	21 (26.9)		23 (26.1)	35 (29.9)	
IgD	5 (2.4)	2 (1.6)	3 (3.8)		2 (2.3)	3 (2.6)	
Light chain	16 (7.8)	12 (9.4)	4 (5.1)		10 (11.4)	6 (5.1)	
Time since diagnosis							
Median time, days (range)	574 (7-2,401)	681 (57-2,355)	430 (7-2,401)	0.0033	561.5 (15-2,355)	660 (7-2,401)	0.4895
ISS stage n (%)							
1	41 (23.4)	26 (22.8)	15 (24.6)	0.7288	17 (22.4)	24 (24.2)	0.7761
2	73 (41.7)	50 (43.9)	23 (37.7)		34 (44.7)	39 (39.4)	
3	61 (34.9)	38 (33.3)	23 (37.7)		25 (32.9)	36 (36.4)	
Laboratory values, median (range)							
Hemoglobin (g/dL)	9.6 (4.9-15.5)	10.2 (4.9-15.5)	8.9 (5.0-13.1)	0.0044	10.1 (5.0-15.4)	9.2 (4.9-15.5)	0.5145
Adjusted serum calcium (mg/dL)	9.6 (7.6-16.7)	9.6 (7.6-15.7)	9.6 (7.9-16.7)	0.8885	9.7 (7.6-16.7)	9.6 (7.9-15.7)	0.0533
Serum creatinine (md/dL)	0.85 (0.33-17.0)	0.85 (0.39-4.90)	0.85 (0.33-17.0)	0.5761	0.84 (0.39-7.34)	0.87 (0.33-17.0)	0.6059
CRAB criteria n (%)							
Hypercalcemia	65 (31.7)	44 (34.6)	21 (26.9)	0.1657	34 (40.5)	31 (27.0)	0.0446
Renal insufficiency	36 (17.6)	21 (16.5)	15 (19.2)	0.7372	14 (16.7)	22 (19.1)	0.6556
Anemia	122 (59.5)	68 (53.5)	54 (69.2)	0.0423	53 (62.4)	69 (60.0)	0.7359
Bone disease	96 (49.8)	71 (63.9)	25 (39.7)	0.0021	59 (74.7)	37 (38.9)	< 0.0001
Novel agents as an induction therapy n (%)	63 (31.7)	63 (49.6)	0 (0)		37 (42.0)	28 (23.9)	0.0058
Novel agents during a clinical course n (%)	127 (62.0)	127 (100)	0 (0)		59 (67.0)	68 (58.1)	0.1926
Treatment regimens of new agents n (%)							
Bortezomib based regimens	77 (37.6)	77 (60.6)	0 (0)		40 (45.5)	37 (31.6)	0.0431
Lenalidomide based regimens	73 (35.6)	73 (57.5)	0 (0)		33 (37.5)	40 (34.2)	0.6241
Thalidomide based regimens	33 (16.1)	33 (25.9)	0 (0)		11 (12.5)	22 (18.8)	0.2242
Autologous stem cell transplant n (%)	21 (10.2)	21 (16.5)	0 (0)		12 (13.6)	9 (7.7)	0.1648

ISS, International Staging System; CRAB, myeloma-related organ dysfunction criteria

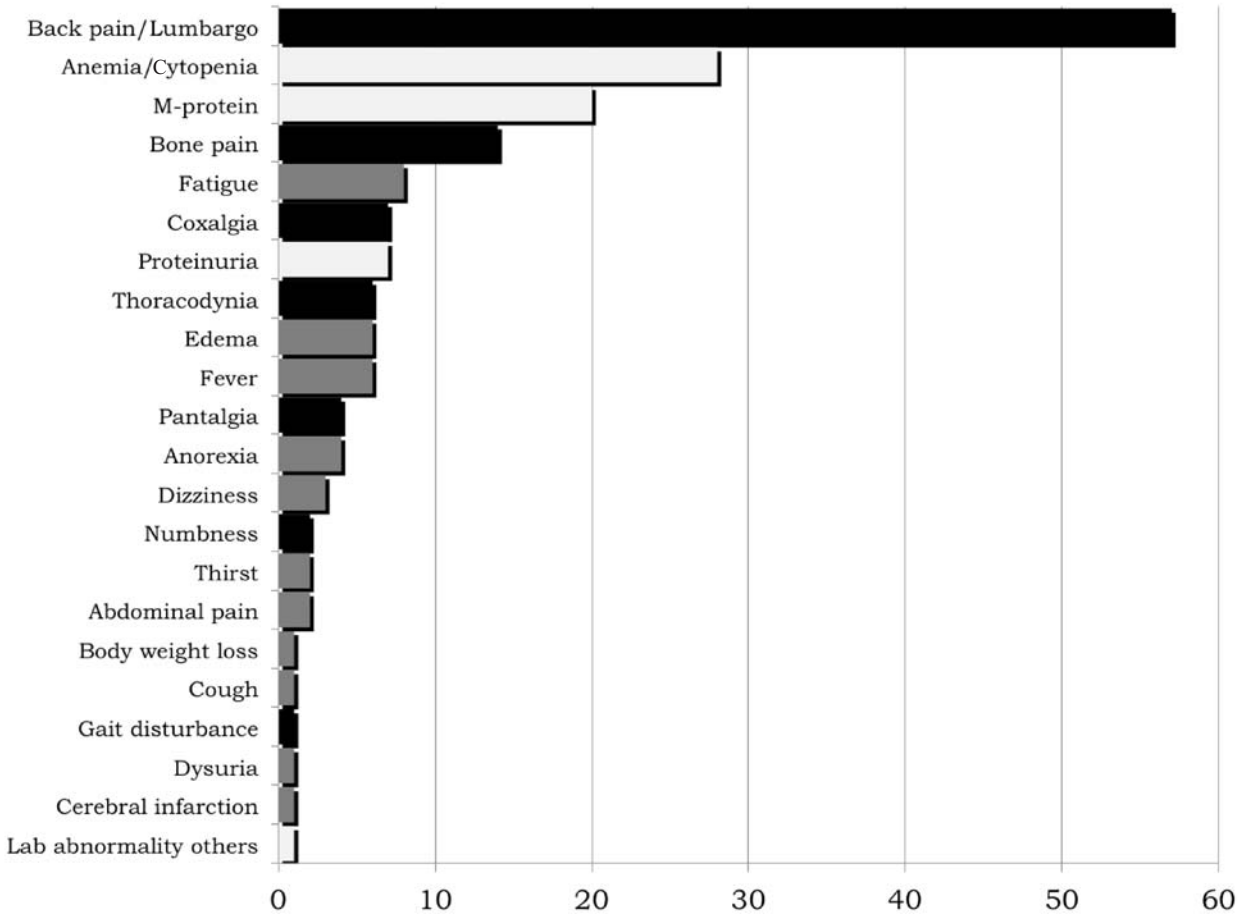

Fig. 1. Symptoms at the time of diagnosis with multiple myeloma, including both subjective symptoms and laboratory abnormalities that were detected without subjective symptoms. *Black* bars represent symptoms related to orthopedic problems, *gray* bars represent nonspecific symptoms, and *white* bars represent laboratory abnormalities without subjective symptoms.

dL) in 17.6% of patients, anemia (hemoglobin level < 10 g/dL) in 59.5% of patients, and bone disease (lytic lesions or osteopenia) in 49.8% of patients (Table 1). Comparing the new-agent group with the conventional chemotherapy group, we observed that bone disease (lytic lesions or osteopenia) was significantly more common in the new-agent group than it was in the conventional chemotherapy group ($P = 0.0021$). We also compared patients who had orthopedic problems at the time of MM diagnosis (orthopedic group, n = 88) with those who did not (non-orthopedic group, n = 117). We examined both patient characteristics and the treatments that were received. Contrary to our expectation, the orthopedic group was younger than the non-orthopedic group (70.0 years vs. 74.0 years, $P = 0.0237$). Hypercalcemia was observed more commonly in the orthopedic group than in the non-orthopedic group (40.5% vs. 27.0%, $P = 0.0446$). New agents were also more commonly administered to patients in the orthopedic group than in the non-orthopedic group ($P = 0.0058$). This was especially true of bortezomib ($P = 0.0431$).

We examined overall survival for the entire cohort of 205 patients who were newly diagnosed with MM. The median survival time was 1,554 days. Log-rank tests were used to assess the impact of the novel agents on overall survival. Patients treated with one or more of the novel agents had longer survival after diagnosis (1,621 days vs. 866 days, $P = 0.0010$). Patients treated with bortezomib were not observed to have a significantly longer median survival time than those treated without it ($P = 0.2398$). However, patients treated with lenalidomide had a significantly longer median survival time than those treated without it (1,850 days vs. 1,023 days, $P = 0.0002$). We additionally divided the patients into 2 groups: those who did and those who did not receive novel agents during induction therapy. Patients who did receive novel agents during induction therapy were observed to have a significantly better median survival time than those who were initially treated with conventional chemotherapy (1,617 days vs. 1,452 days, $P = 0.0454$). Moreover, multivariate

analysis was performed to determine the effect of all factors examined in the univariate analysis. The stepwise multivariate Cox proportional hazards analysis revealed that the use of novel agents as induction therapy was independently associated with improved survival ($P = 0.049$; HR for death, 0.479; 95% CI, 0.230-0.999). Age at diagnosis ($P < 0.001$; HR, 1.059; 95% CI, 1.030-1.088), renal insufficiency at diagnosis ($P = 0.003$; HR, 2.750; 95% CI, 1.418-5.330), and ISS category (1 vs. other; $P = 0.005$; HR, 0.268; 95% CI: 0.107-0.671) were also independently associated with survival (Table 2). No significant interactions between age, ISS, renal insufficiency, and time-induction therapy were demonstrated in our Cox regression results ($P = 0.339$).

In the present study, we investigated the outcomes of patients in Japan who had newly diagnosed MM during the era of novel agents. Previously, a large cohort study investigated the same topic at the Mayo Clinic, in the United States, during 2001-2006.[3] There is a close resemblance between Kaplan-Meier survival estimates that were found in the present study and those found in the Mayo Clinic study. Moreover, we found that, in Japanese general practice, MM patients who received the novel agents as induction therapy had better survival rates than those who received conventional chemotherapy. This finding is consistent with randomized trials in several nations.[5-9] Although the novel agents were approved several years earlier in Western countries than in Japan, both Japanese and Western patients with MM are currently being treated with novel agents.

In this analysis, the median age was 6 years older than that reported in a previous study.[11] This discrepancy could be associated with the older age distribution of Akita residents; in Akita, 44% of residents were over 65 years of age as of 2012. Moreover, the incidence of newly diagnosed symptomatic MM in an average year was estimated to be approximately 3 per 100,000 individuals in Akita prefecture. (We were able to calculate this estimate because the 12 major hospitals that participated in this study cover the population of Akita prefecture, which is close to 1 million.) The overall incidence of MM in Akita prefecture seems to be slightly higher than the average overall incidence of MM in Japan,[2] probably for the same reason. Even in other countries, the incidence rates of MM are clearly elevated by aging.[14]

At the time of diagnosis with MM, hypercalcemia was observed in 5.6% of patients in a large Japanese cohort.[11] In the present study, however, hypercalcemia was observed in 31.7% of patients at the time of diagnosis with MM. Although the cause of this discrepancy is unknown, the percentage of patients with hypercalcemia at diagnosis ranges from 13% to 32% in Western countries, which is similar to our findings.[15,16] In previous studies, renal insufficiency and anemia were observed in 20% and 73% of patients with newly diagnosed multiple myeloma, respectively.[15] In the present study, these conditions were observed in 17.6% and 59.5% of patients, respectively, at diagnosis; these values are consistent with those of previous reports. Although bone lesions were previously observed in almost 80% of patients with newly diagnosed multiple myeloma,[15] approximately half of the patients in our study had these lesions. On the other hand, 25% of the patients experienced no subjective symptoms and were only diagnosed on the basis of laboratory abnormalities. This frequency of asymptomatic diagnosis is much greater than we had expected, and may be the principal reason why bone abnormalities were less common in our study than in previous reports. The present study included no patients with monoclonal gammopathy of undetermined significance or smoldering multiple myeloma; the incidences of these diseases and the rates of progression to MM should be clarified in the future.

Table 2. Prognostic factors for overall survival

Clinical data	Hazard ratio (95% CI)	*P* - value
Age at diagnosis	1.059 (1.030-1.088)	< 0.001
Renal insufficienty at diagnosis	2.750 (1.418-5.330)	0.003
International stage system (1 vs 2/3)	0.268 (0.107-0.671)	0.005
Upfront novel agents	0.479 (0.230-0.999)	0.049

Ohguchi *et al*.[17] reported that β_2-microglobulin is an independent prognostic marker for MM treatment using bortezomib. However, their study was retrospective and included a small number of patients. On the other hand, Kaneko *et al*. reported that age and C-reactive protein values were both independently predictive of survival before the era of novel agents.[18] In the present analysis, the independent risk factors at diagnosis were confirmed using Cox proportional hazards regression: age, renal insufficiency (serum creatinine level > 2.0 mg/dL), and staging according to the International Staging System (ISS) standard for MM.[19] ISS guidelines define 3 risk groups based on albumin and serum β_2-microglobulin, which is closely related to both renal function and tumor mass.[19] Although the ISS classification system is quite simple, our findings suggest that it is a useful means of assessing prognosis for patients with MM, even in the era of novel agents. Importantly, the use of novel agents as induction therapy was found to be independently predictive of survival. According to this analysis, each additional year of age led to a 1.059-fold increase in the risk of death among patients with MM. Renal insufficiency at diagnosis led to a 2.750-fold increase in the risk of death. On the other hand, stage 1 MM was associated with an HR of 0.268, and the use of novel agents as induction therapy was associated with an HR of 0.479. Both stage 1 MM and novel agents were associated with significantly increased survival.

Although this study was retrospective and incorporated only a small portion of Japan, our data constituted a population-based cohort that included almost the entirety of Akita prefecture. Therefore, the results of this study exactly

reflect daily practice in Akita prefecture. Moreover, this is the first large multicenter study to evaluate new agents in Japan. We found that patients with MM who received novel agents had better prognoses than patients who received conventional chemotherapy. The results of our Cox regression analysis particularly suggest that induction therapy using novel agents may confer a survival benefit. A large prospective study is necessary to confirm these findings.

REFERENCES

1 Kyle RA, Rajkumar SV: Multiple myeloma. Blood 111:2962-2972, 2008

2 Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, *et al*.: Cancer incidence and incidence rates in Japan in 2003: based on data from 13 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. Jpn J Clin Oncol 39:850-858, 2009

3 Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, *et al*.: Improved survival in multiple myeloma and the impact of novel therapies. Blood 111:2516-2520, 2008

4 Myeloma Trialists' Collaborative Group: Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. J Clin Oncol 16:3832-3842, 1998

5 Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, *et al*.: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 352:2487-2498, 2005

6 Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, *et al*.: Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 357:2123-2132, 2007

7 Weber DM, Chen C, Niesvizky R, Wang M, Belch A, *et al*.: Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 357:2133-2142, 2007

8 San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, *et al*.: Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 359:906-917, 2008

9 Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, *et al*.: Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. J Clin Oncol 28:2259-2266, 2010

10 Facon T, Dimopoulos MA, Dispenzieri A, Catalono J, Belch AR, *et al*.: Initial phase 3 results of the first (Frontline Investigation of Lenalidomide+Dexamethasone versus Standard Thalidomide) trial (MM-020/IFM 0701) in newly diagnosed multiple myeloma patients ineligible for stem cell transplantation. Blood (ASH Annual Meeting Abstracts) 122:2, 2013 [abstract]

11 Shimizu K, Nagura E, Takatsuki K: Management of patients with multiple myeloma in Japan: data of 1,383 patients from 16 hospitals and 1 treatment group. Leuk Lymphoma 45:2465-2469, 2004

12 Chou T: Multiple myeloma: recent progress in diagnosis and treatment. J Clin Exp Hematop 52:149-159, 2012

13 Kyle RA, Rajkumar SV: Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 23:3-9, 2009

14 Phekoo KJ, Schey SA, Richards MA, Bevan DH, Bell S, *et al*.: A population study to define the incidence and survival of multiple myeloma in a National Health Service Region in UK. Br J Haematol 127:299-304, 2004

15 Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, *et al*.: Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 78:21-33, 2003

16 Wisloff F, Kvam AK, Hjorth M, Lenhoff S: Serum calcium is an independent predictor of quality of life in multiple myeloma. Eur J Haematol 78:29-34, 2007

17 Ohguchi H, Sugawara T, Ishikawa I, Okuda M, Tomiya Y, *et al*.: A retrospective analysis of bortezomib therapy for Japanese patients with relapsed or refractory multiple myeloma: β_2-microglobulin associated with time to progression. Int J Hematol 89:342-347, 2009

18 Kaneko M, Kanda Y, Oshima K, Nannya Y, Suguro M, *et al*.: Simple prognostic model for patients with multiple myeloma: a single-center study in Japan. Ann Hematol 81:33-36, 2002

19 Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, *et al*.: International staging system for multiple myeloma. J Clin Oncol 23:3412-3420, 2005