Journal of clinical and experimental hematopathology
Vol. 57 No.2, 47-53, 2017

Original article

Characteristics and Prognosis of Patients with Immunoglobulin M Monoclonal Gammopathy

Hiroaki Tanaka,[1)] Yukie Sakuma,[2)] Hideki Ikeda,[3)] Ryo Shimizu,[1)] Yasumasa Sugita,[1)] and Rie Iwai[4)]

Many patients with immunoglobulin M (IgM) monoclonal gammopathy remain asymptomatic and, consequently, untreated; however, few studies have evaluated the clinical course and prognosis of these patients. Using the screening procedures at our hospital, 74 patients with IgM monoclonal gammopathy were selected. We excluded 11 patients in whom the treatment for lymphoid neoplasms had been initiated at the time of IgM monoclonal protein detection. The remaining 63 patients were considered to be the patient population with IgM MGUS and asymptomatic WM, and were analyzed. In these patients, the median overall survival was longer than 14 years. More than half of these patients died from causes other than lymphoid neoplasm. The cumulative incidence of lymphoid neoplasm requiring treatment was 17.5%. In five of eight patients requiring treatment for lymphoid neoplasms, the causes of death were related with these lymphoid neoplasms. Our study suggests that not all patients with IgM monoclonal gammopathy require uniform treatment for prolonged survival; however, most lymphoid neoplasms requiring treatment are refractory diseases. Our findings may help manage patients with macroglobulinemia.

Keywords: IgM monoclonal gammopathy, IgM monoclonal gammopathy of undetermined significance, Waldenstrom macroglobulinemia

INTRODUCTION

Immunoglobulin M (IgM) monoclonal gammopathy is detected in patients with IgM monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom macroglobulinemia (WM), other indolent B-cell lymphomas, and IgM amyloidosis.[1,2] Most patients with IgM monoclonal gammopathy remain asymptomatic and, consequently, untreated[1,3,4]; however, as such patients are relatively rare and have long clinical courses, there are fewer studies analyzing the clinical course and prognosis of patients with IgM monoclonal gammopathy. Furthermore, as monoclonal gammopathy is examined only when there are symptoms or clinical findings that raise suspicion of its presence, the number of patients with IgM monoclonal gammopathy who are undiagnosed because of the asymptomatic course of the disease remains unknown.

At our hospital, screening for monoclonal gammopathy was included in the serological testing for all patients examined for either total protein (TP) or by both the thymol turbidity test (TTT) and the zinc sulfate turbidity test (ZTT) between 1990 and 2010.

In this study, we retrospectively analyzed these data to clarify the type of lymphoid neoplasms that developed in patients with IgM monoclonal gammopathy, their prognoses, and their causes of death.

MATERIALS AND METHODS

Study design

At our hospital, screening for monoclonal gammopathy was included in the serological testing for all patients examined for TP or by both TTT and ZTT between 1990 and 2010. Accordingly, with the approval from the hospital's ethics committee in November 2015, we retrospectively analyzed the clinical course of patients with IgM monoclonal gammopathy.

Screening and confirmation of monoclonal protein

Protein electrophoresis examination was performed on all patients who met one of the following criteria: (1) TP ≥ 8 g/dL; (2) until 1996, in patients with normal levels of both aspartate aminotransferase and alanine aminotransferase, TTT ≤ 0.9 U and ZTT ≥ 12.0 U, or TTT ≤ 0.5 U, ZTT ≤ 5.0 U, and A/G < 1.0; since 1996, a difference between ZTT and

Received: May 27, 2017. Revised: August 29, 2017. Accepted: September 4, 2017.
[1)]Department of Hematology, Asahi General Hospital, Chiba, Japan, [2)]Clinical Research Support Center, Asahi General Hospital, Chiba, Japan, [3)]Department of Internal Medicine, Asahi General Hospital, Chiba, Japan, [4)]Department of Transfusion Medicine, Asahi General Hospital, Chiba, Japan
Corresponding author: Hiroaki Tanaka, M.D., Ph.D., Department of Hematology, Asahi General Hospital I-1326, Asahi-city, Chiba, Japan 289-2511. E-mail: htanaka@hospital.asahi.chiba.jp

TTT of ≥10 U or ≤1 U; the product of ZTT × TTT is ≥10 U or ≤1 U; or the quotient of ZTT/TTT is ≥200 U or ≤1 U; (3) request for protein electrophoresis examination. If monoclonal gammopathy was suspected after protein electrophoresis, it was confirmed by immunoelectrophoresis.

At our hospital, 10,608 serum/plasma-samples were screened and 1388 protein electrophoreses were measured every year on average; a total of 222,771 serum/plasma-samples were estimated and a total of 29,150 protein electrophoreses were measured, respectively, in the 21 years between 1990 and 2010.

Patients

The screening between 1990 and 2010 revealed a total of 1,486 patients with monoclonal gammopathy, including 74 patients with IgM monoclonal gammopathy. We excluded 11 patients in whom the treatment for lymphoid neoplasms had been initiated at the time of IgM monoclonal protein detection. The remaining 63 patients were considered to be the patient population with IgM MGUS and asymptomatic WM, and were analyzed for overall survival, cause of death, and cumulative incidence of requiring treatment. These 63 patients were monitored for 410 person-years (median, 2080 days; range, 1–7010 days) for overall survival and for 363 person-years (median, 1753 days; range, 1–7010 days) for cumulative incidence of requiring therapy for lymphoid malignancies.

Statistics

Overall survival was defined as the time from the first detection of IgM monoclonal protein to death from any cause. The survival curves were determined by the Kaplan–Meier method. To compare the differences between the survival curves, the log-rank test was used. In the multivariate analysis, Cox proportional hazards regression was performed. The cumulative incidence of requiring treatment and comparison of the differences among the cumulative incidences were evaluated using Gray's method by considering death before treatment as a competing risk. Factors analyzed for influence on overall survival and cumulative incidence in the univariate analysis were as follows: male; an age of ≥70 years at the first detection of IgM monoclonal protein; total protein of ≥8.5 g/dL; albumin level of ≤3.5 g/dL; hemoglobin level of ≤10 g/dL; platelet count of ≤15 × 10^4/μL; amount of monoclonal protein ≥2 g; IgM of >1000 mg/dL; IgG of ≤1000 mg/dL; IgA of ≤150 mg/dL; lactate dehydrogenase of ≥300 U/L; alkaline phosphatase of ≥300 U/L; and creatinine level of >1 mg/dL. A *p*-value of less than 0.05 was considered significant. All statistical analyses were performed with EZR software (Saitama Medical Centre, Jichi Medical University, Japan; http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html; Kanda, 2012), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0). More precisely, it is a modified version of the R commander (Version 1.6–3) that was designed to add statistical functions frequently used in biostatistics.[5]

RESULTS

Patient characteristics

The patient characteristics are shown in Table 1. The median age of the patients during the detection of IgM monoclonal protein was 72 years (range, 1–94 years), and 45 (71.4%) patients were males. The median number of observation days was 2088 days (range, 1–7010 days).

In patients with IgM monoclonal protein, there were three patients with refractory pleural effusion after the detection of IgM monoclonal protein. Two of them underwent pleural biopsy. One of these two patients was diagnosed with marginal zone lymphoma and the other died of respiratory failure without a definite diagnosis. The third patient had been treated for cold agglutinin disease (CAD) for over 50 years and was suspected to have indolent lymphoma because of the cytology of the pleural effusion; however, a definitive diagnosis was not reached and the patients were transferred to the recuperation hospital.

Overall survival and cause of death

A total of 20 patients died during the observation period. The median overall survival was 5180 days [95% confidence interval (CI) 3340–NA days]. The 10-year survival rate was 64.4% (95% CI 47.7–77.0%) (Figure 1).

Lymphoid neoplasms were the cause of death in four

Table 1. Characteristics of patients with IgM MGUS and asymptomatic WM (n=63)

Age at detection (median, range)	72 (1–94) years
Male/female	45/18
Observation duration (median, range)	2088 (1–7010) days
Amount of monoclonal protein	1.59 (0.67–5.37) g/dL
Only heavy chain	19 patients
Kappa chain	23 patients
Lambda chain	21 patients
IgM	735 (56–8180) mg/dL
IgG	1150 (257–2841) mg/dL
IgA	196 (12–1519) mg/dL
Total protein	7.4 (5.3–9.8) g/dL
Albumin	4.0 (2.3–4.9) g/dL
Hemoglobin	13.05 (3.5–16.4) g/dL
Platelet	21.9 (8.2–207) × 104/μL
Lactate dehydrogenase	217.5 (117–1909) U/L
Alkaline phosphatase	240.5 (101–1438) U/L

The case with hemoglobin level 3.5 g/dL had anemia due to cold agglutinin disease.

patients (20.0%), including WM in one patient, diffuse large B-cell lymphoma (DLBCL) in one, and lymphoma of unknown classification in two. Hematological disease other than lymphoid neoplasms, including acute myeloid leukemia (AML) in one patient and MDS in another, was the cause of death in two patients. Solid tumors, including colon cancer, breast cancer, and bile duct cancer, were the cause of death in three patients, respectively. Heart disease was the cause of death in three patients, stroke in two patients, pneumonia or respiratory failure in three patients, and sudden death or death from senility in three patients (Table 2).

Influencing factors for overall survival

In the univariate analysis, an age of ≥70 years-old, an albumin level of ≤3.5 g/dL, a hemoglobin level of ≤ 10 g/dL, and a TP of ≥8.5 g/dL at the first detection of IgM monoclonal protein were significantly associated with a poor prognosis ($p < 0.01$, $p < 0.01$, $p = 0.03$, and $p = 0.03$, respectively) (Figure 2). Multivariate analysis of these four factors revealed that an age of >70 years-old and TP ≥8.5 g/dL at the first detection of IgM monoclonal protein were independently correlated with a poor prognosis ($p = 0.01$ and $p = 0.02$, respectively) (Table 3).

The cumulative incidence of requiring treatment for lymphoid malignancies and influencing factors

Eight patients who required treatment for lymphoid neoplasms after detection of IgM monoclonal protein (median age at detection, 68 years (range, 56–92 years), seven (87.5%) males) are shown in Table 4. The median duration from the detection of IgM monoclonal protein to the initiation of treatment was 1145 days (range, 39–2213 days). The cumulative incidence of requiring treatment was 17.5% using Gray's method (Figure 3a). In the univariate analysis, only the amount of monoclonal protein ≥2 g was significantly correlated with a high incidence of requiring treatment ($p = 0.04$) (Figure 3b). There were four patients with WM: a patient with MALT lymphoma, one with marginal zone lymphoma, one with DLBCL, and one with AITL. Therapies and the outcomes for lymphoid neoplasms among eight patients are shown in Table 4

Six of the eight patients died during the observation period. The median duration from the initiation of treatment to death was 2241 days (range, 52–3406 days). The causes of death were lymphoid neoplasms in three patients, and AML, myelodysplastic syndrome (MDS), and acute myocardial infarction in one of the remaining three patients each. The patients with AML and MDS had been administered oral chemotherapies (cyclophosphamide or MP therapy) for at least 5 years.

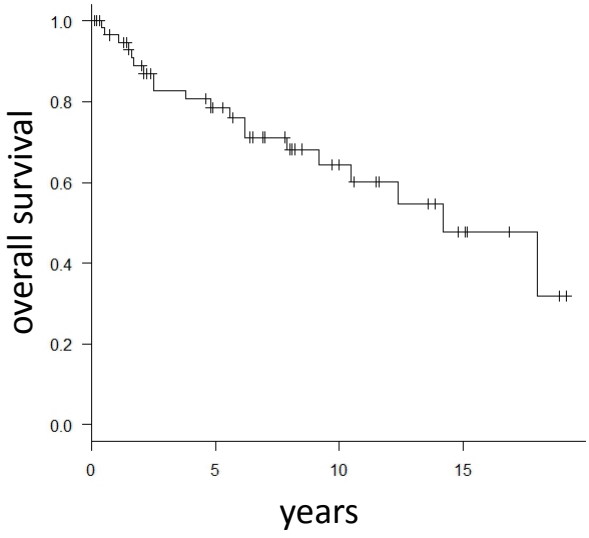

Fig. 1. Overall survival curve.

DISCUSSION

As the subjects of our study were extracted by screening procedures, it has a relatively small bias and is similar with epidemiological studies because the patients with monoclonal protein were identified by screening when they visited our hospital for different purposes, including cases health

Table 2. 20 patients who died during observation period

Age at the detection (median, range)	72.5 (56–94) years-old
Male/female	17/3
Duration from the detection to death (median, range)	1571 (149–6583) days
Cause of death	
Lymphoid neoplasm	4 patients (20.0%)
WM	1
DLBCL	1
Unknown	2
Other hematological disease	2 patients (10.0%)
Acute myeloid leukemia	1
Myelodysplastic syndrome	1
Solid tumor	3 patients (15.0%)
Colon cancer	1
Breast cancer	1
Vile duct cancer	1
Other cause	11 patients (55.0%)
Heart disease	3
Stroke	2
Pneumonia or respiratory failure	3
Sudden death or death of senility	3

WM, Waldenstrom macroglobulinemia; DLBCL, Diffuse large B-cell lymphoma.

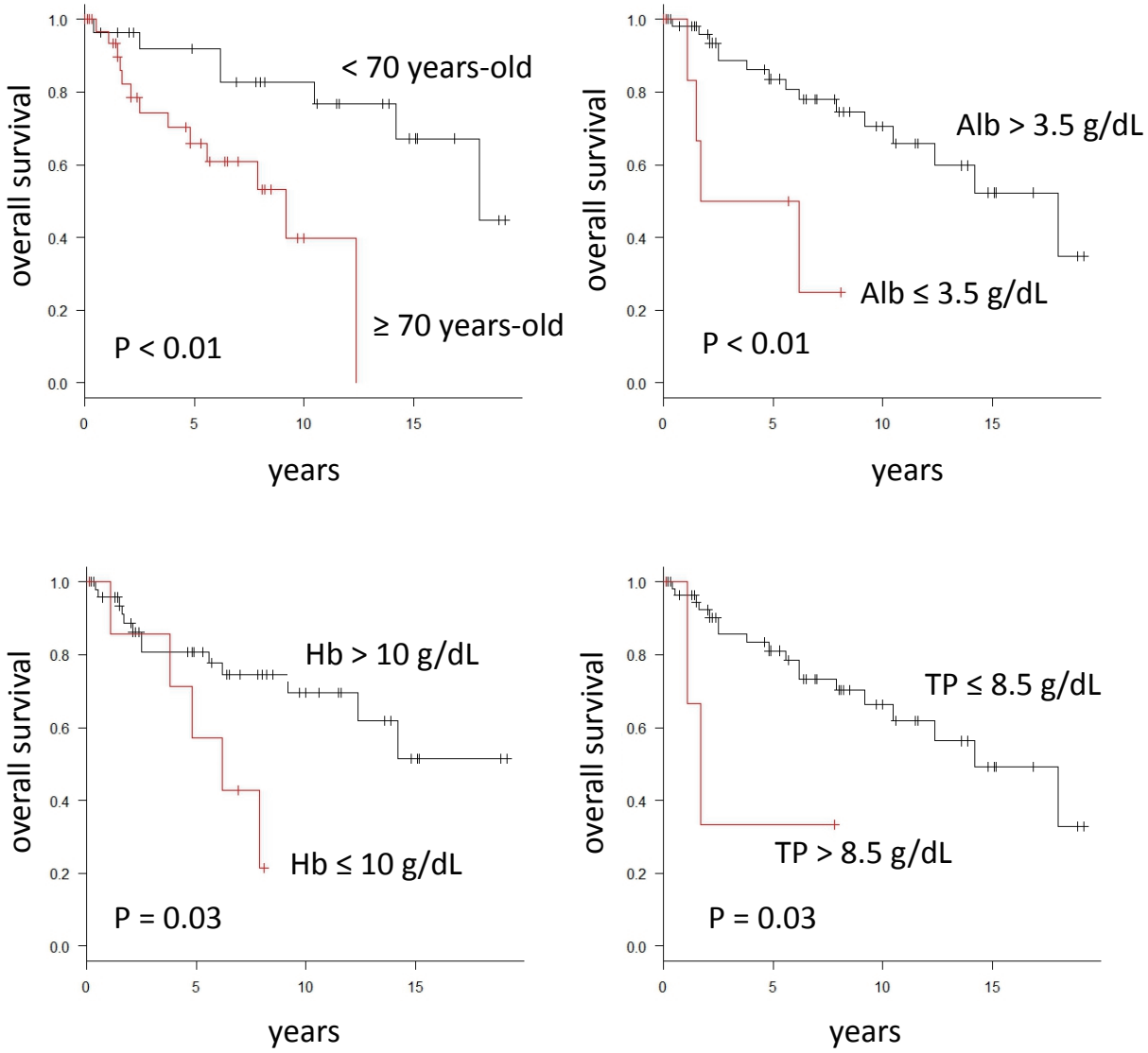

Fig. 2. In the univariate analysis, an age of ≥70 years, albumin level of ≤3.5 g/dL, hemoglobin level of ≤10 g/dL, and total protein of ≥8.5 g/dL at the first detection of IgM monoclonal protein were significantly correlated with a poor prognosis ($p < 0.01$, $p < 0.01$, $p = 0.03$, and $p = 0.03$, respectively).

Table 3. Multivariate analysis of influencing factors for overall survival

	Hazard ratio	95%CI	p-value
Total protein > 8.5 g/dL	7.20	1.44–35.56	0.02
>70 years-old	4.70	1.41–15.64	0.01

examinations.

The limitation of our study is that because the patients with monoclonal protein were identified by screening, most of the 63 patients with IgM MGUS and asymptomatic WM were not closely examined for hematological disease when IgM monoclonal protein was first detected. Furthermore, as bone marrow examination was not performed on most of these patients at the time of IgM monoclonal protein detection, these patients were unable to be separated into IgM MGUS and asymptomatic WM by International myeloma working group.[6] Baldini *et al.*[7] found that both IgM MGUS and asymptomatic WM have the same determinants related to evolution, and devised a scoring system to identify subsets of patients affected by "asymptomatic macroglobulinemias" integrated from IgM MGUS and asymptomatic WM. We considered the 63 patients to have "asymptomatic IgM monoclonal gammopathy", which consists of IgM MGUS and asymptomatic WM, and analyzed the overall survival and cumulative incidence of requiring treatment.

As an epidemiologic study of MGUS in Japan, there was a study for survivors of atomic bomb detonation[8], which reported that the overall prevalence of MGUS was 2.1% and that IgM MGUS comprised 7.5% of all MGUS, and had a significantly higher prevalence in men than in women. In our study, the screening between 1990 and 2010 revealed a total of 1,486 patients with monoclonal gammopathy.

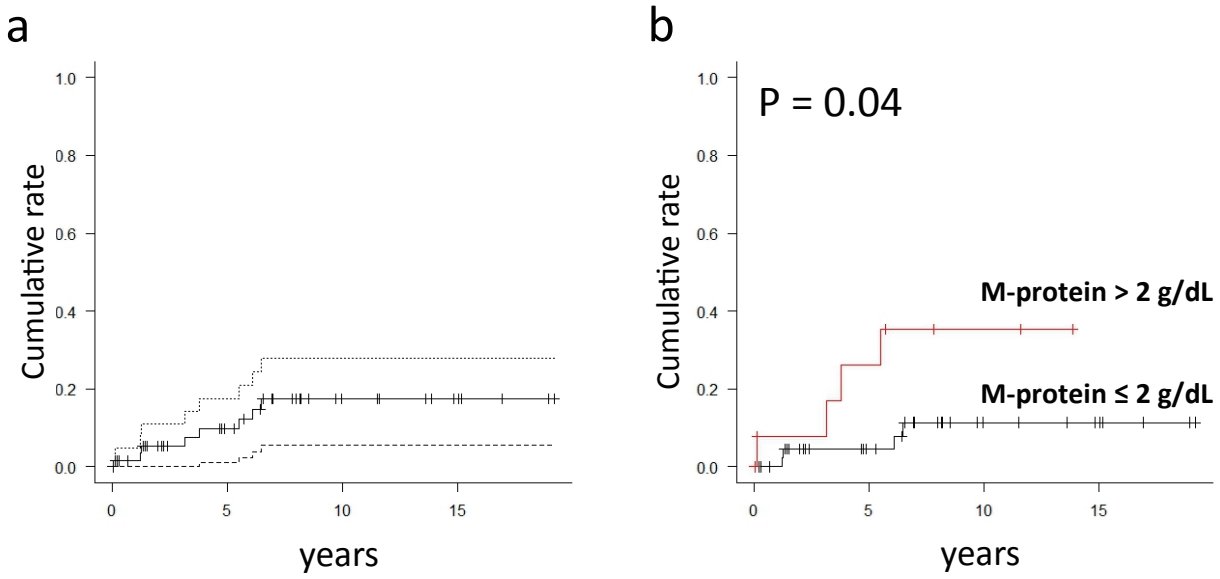

Fig. 3. Cumulative incidence curve of requiring treatment (***1a***). In the univariate analysis, only the amount of monoclonal protein ≥2 g was significantly correlated with a high cumulative incidence of requiring treatment (***1b***).

Table 4. Eight patients who required treatment for malignant lymphoma after the detection of IgM monoclonal protein

Age at detection	sex	disease	therapy to treatment	duration to Tx	outcome (days after Tx)	cause of death
64	m	WM	MP	2354	D (4229)	AML
56	m	WM	CY, MP	3823	D (2678)	MDS
64	m	WM	CY, Flu, R, Ben	2213	D (2967)	lymphoma
69	f	AITL	CP	39	D (2241)	AMI
92	m	DLBCL	VP16	431	D (130)	lymphoma
64	m	MALT	R-CHOP	459	A (3406)	-
71	m	WM	Flu	2004	D (52)	lymphoma
68	m	MZL	CP	2999	A (1625)	-

WM, Waldenstrom macroglobulinemia; MALT, mucosa associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; CY, cyclophosphamide; CP, cyclophosphamide and prednisolone; MP, melphalan and prednisolone; VP16, etoposide; R-CHOP, rituximab, cyclophosphamide, vincristine, and prednisolone; AML, acute myeloid leukemia; MDS, myelodysplasitic syndrome; AMI, acute myocardial infarction; D, dead; A, alive.

Unfortunately, the overall prevalence of monoclonal gammopathy was not confirmed because we were unable to obtain the number of screened patients. We confirmed in our study that IgM monoclonal gammopathy comprised 5.0% of all types and that the prevalence was higher in men than in women.

According to our results, similar with previous reports[2, 9-12], most of the lymphoid neoplasms developing in patients with IgM monoclonal gammopathy were indolent B-cell lymphomas and there were no cases of multiple myeloma; however, there was one instance of AITL in the 63 patients with IgM monoclonal protein. The patient was diagnosed 53 days after the detection of IgM monoclonal protein. AITL often complicates secondary B-cell lymphoid neoplasms, many of which are associated with Epstein–Barr virus because of the underlying immune dysfunction.[13] Lin *et al*. also reported four patients with AITL in 382 patients with lymphoid neoplasms associated with IgM monoclonal gammopathy.[2] We tend to assume that patients with IgM monoclonal protein develop indolent B-cell lymphoma; however, AITL should also be taken into consideration.

In our study, there were three patients with refractory pleural effusion after the detection of IgM monoclonal protein. For two, a definite diagnosis could not be reached, and one was suspected of indolent lymphoma from the cytology results for the pleural effusion. IgM monoclonal protein was detected in most patients with primary CAD and represents a spectrum of clonal lymphoproliferative bone marrow disorders.[14] Some of these patients develop lymphomas during their long clinical course.[15]

In our study, the median overall survival was over 14 years. In only one-fifth of these patients, lymphoid

neoplasms were the cause of death, and more than half of these patients died from causes completely unrelated with lymphoid neoplasms. Our study suggested that all patients with IgM monoclonal gammopathy do not require uniform treatment for prolonged survival. No data are available to justify the early initiation of treatment, and patients with asymptomatic macroglobulinemia should be followed without therapy.[16] In the multivariate analysis, an age of >70 years and a TP of ≥8.5 g/dL at the first detection of IgM monoclonal protein were independently correlated with a poor prognosis. The amount of monoclonal protein, which is one of the indicators of tumor burden from lymphoid neoplasms, was not associated with a poor prognosis even by univariate analysis.

Our study found that the cumulative incidence of requiring treatment for lymphoid malignancies was 17.5%. In contrast to the results of overall survival, the amount of monoclonal protein was the only significant factor associated with a high incidence of requiring treatment for lymphoid malignancies. The study by Baldini *et al*.[7] reported that 6.9% of the 217 patients with IgM MGUS required chemotherapy after a median follow-up of 56.1 months, and 22.4% of the 201 patients with asymptomatic WM required chemotherapy after a median follow-up of 60.2 months. The variables inversely correlated with evolution were the amount of IgM monoclonal protein, the hemoglobin level, and gender (male or female). In a report of 213 patients with IgM MGUS[9], the cumulative incidence of progression to lymphoma or a related disorder was 10% at 5 years, 18% at 10 years, and 24% at 15 years. The monoclonal protein and albumin concentrations at diagnosis were the only risk factors. In another report on 242 patients with IgM MGUS[10], malignant lymphoid disorders developed in 40 (17%) patients at an average of 4 years after detection of the monoclonal protein. In another report on 26 patients with IgM MGUS[11], macroglobulinemia (four patients), lymphoma (three patients), and chronic lymphocytic leukemia (one patient) developed during a follow-up of 5–20 years. Four cases of macroglobulinemia were diagnosed at a median of 6 years after the recognition of MGUS, whereas MGUS was present for 6, 13, and 15 years in three patients in whom malignant lymphoma developed. In a study on 48 patients with asymptomatic WM[17], the cumulative probability of progression to symptomatic lymphoid neoplasms was 59% at 5 years and 68% at 10 years. The major risk factors for progression were the percentage of lymphoplasmacytic cells in the bone marrow, the amount of monoclonal protein, and the hemoglobin level. In the Southwest Oncology Group-S9003 study[18], of the 59 patients with WM who were initially observed, only 12 patients (21%) required therapy at a median follow-up of 100 months. The only variable at baseline predictive of therapy requirement was the hemoglobin level.

Among the eight patients requiring treatment for lymphoid malignancies in our study, three died of lymphoid neoplasms and two died of secondary myeloid malignancy because of the long-term use of oral cytotoxic agents for lymphoid neoplasms. Although the median duration from requiring treatment for lymphoid malignancies to death was over 6 years, most patients requiring treatment were considered to have refractory disease. Nowadays, it is the general consensus that the first-line therapy for WM should consist of rituximab either alone or preferably in combination.[16] Long-term administration of oral cytotoxic agents is associated with the development of secondary AML and MDS.

In conclusion, our study suggested that not all patients with IgM monoclonal gammopathy required uniform treatment for prolonged survival; however, for many patients with lymphoid neoplasms requiring treatment, it is a refractory disease. Our findings may help to manage patients with macroglobulinemia.

ACKNOWLEDGMENTS

The authors would like to thank Yasunori Sato of the Clinical Research Center and Chikako Ohwada of the Department of Hematology, Chiba University Hospital, Chiba, Japan for their valuable advice on statistics and research design.

CONFLICT OF INTEREST

The authors disclose no potential conflict of interest.

REFERENCES

1 Hobbs JR, Carter PM, Cooke KB, Foster M, Oon CJ : IgM paraproteins. J Clin Pathol Suppl 6 : 54-64, 1975
2 Lin P, Hao S, Handy BC, Bueso-Ramos CE, Medeiros LJ : Lymphoid neoplasms associated with IgM paraprotein : a study of 382 patients. Am J Clin Pathol 123 : 200-205, 2005
3 Oza A, Rajkumar SV : Waldenstrom macroglobulinemia : prognosis and management. Blood Cancer J 5 : e394, 2015
4 Vijay A, Gertz MA : Waldenstrom macroglobulinemia. Blood 109: 5096-5103, 2007
5 Kanda Y : Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48:452-458, 2013
6 International Myeloma Working Group : Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 121 : 749-757, 2003
7 Baldini L, Goldaniga M, Guffanti A, Broglia C, Cortelazzo S, *et al*. : Immunoglobulin M monoclonal gammopathies of undetermined significance and indolent Waldenstrom's macroglobulinemia recognize the same determinants of evolution into symptomatic lymphoid disorders: proposal for a common prognostic scoring system. J Clin Oncol 23:4662-4668, 2005
8 Iwanaga M, Tagawa M, Tsukasaki K, Kamihira S, Tomonaga M: Prevalence of monoclonal gammopathy of undetermined significance : study of 52,802 persons in Nagasaki City, Japan. Mayo Clin Proc 82 : 1474-1479, 2007
9 Kyle RA, Therneau TM, Rajkumar SV, Remstein ED, Offord JR, *et al*. : Long-term follow-up of IgM monoclonal gammopa-

thy of undetermined significance. Blood 102 : 3759-3764, 2003
10 Kyle RA, Garton JP : The spectrum of IgM monoclonal gammopathy in 430 cases. Mayo Clin Proc 62 : 719-731, 1987
11 Pasqualetti P, Festuccia V, Collacciani A, Casale R : The natural history of monoclonal gammopathy of undetermined significance. A 5- to 20-year follow-up of 263 cases. Acta Haematol 97 : 174-179, 1997
12 Owen RG, Parapia LA, Higginson J, Misbah SA, Child JA, *et al*. : Clinicopathological correlates of IgM paraproteinemias. Clin Lymphoma 1 : 39-43, 2000
13 Attygalle AD, Kyriakou C, Dupuis J, Grogg KL, Diss TC, *et al*. : Histologic evolution of angioimmunoblastic T-cell lymphoma in consecutive biopsies : clinical correlation and insights into natural history and disease progression. Am J Surg Pathol 31 : 1077-1088, 2007
14 Berentsen S, Ulvestad E, Langholm R, Beiske K, Hjorth-Hansen H, *et al*. : Primary chronic cold agglutinin disease : a population based clinical study of 86 patients. Haematologica 91 : 460-466, 2006
15 Tanaka H, Hashimoto S, Sugita Y, Sakai S, Takeda Y, *et al*. : Occurrence of lymphoplasmacytic lymphoma 6 years after amelioration of primary cold agglutinin disease by rituximab therapy. Int J Hematol 96 : 501-505, 2012
16 Dimopoulos MA, Kastritis E, Owen RG, Kyle RA, Landgren O, *et al*. : Treatment recommendations for patients with Waldenstrom macroglobulinemia (WM) and related disorders : IWWM-7 consensus. Blood 124 : 1404-1411, 2014
17 Kyle RA, Benson JT, Larson DR, Therneau TM, Dispenzieri A, *et al*. : Progression in smoldering Waldenstrom macroglobulinemia : long-term results. Blood 119 : 4462-4466, 2012
18 Dhodapkar MV, Hoering A, Gertz MA, Rivkin S, Szymonifka J, *et al*. : Long-term survival in Waldenstrom macroglobulinemia : 10-year follow-up of Southwest Oncology Group-directed intergroup trial S9003. Blood 113 : 793-796, 2009