Mantle Cell Lymphoma in Thai Patients

Tanin Intragumtornchai MD, MSc*, Ponlapat Rojnuckarin MD, PhD*,
Pranee Sutcharitchan MD*, Pongsak Wannakrairot MD**

** Department of Medicine, Faculty of Medicine, Chulalongkorn University*
***Department of Pathology, Faculty of Medicine, Chulalongkorn University*

Mantle cell lymphoma (MCL) is a disease entity recently introduced into the new lymphoma classification, therefore, the clinical features as well as therapeutic outcomes in Thai patients with MCL has never been described. The authors herein retrospectively analysed 21 newly diagnosed patients with MCL at King Chulalongkorn Memorial Hospital from January 1997 to December 2002. The median age of the patients was 54 years (range, 38-79). Male:female was 4:1. Generalized lymphadenopathy (67%) was the most common presenting feature. The majority of patients (85%) had advanced disease (stage III, IV, Ann Arbor system). Fifty-six percent of the patients were classified as the high- and high-intermediate risk group by the international prognostic index. Most patients were treated with CHOP (vincristine, cyclophosphamide, doxorubicin, prednisolone) or CVP (vincristine, cyclophosphamide, prednisolone) regimen. The overall complete remission rate was 59%. With a median follow-up of 13 months (range, 1-62 months), the rates of overall, progression-free and disease-free survivals were 32%, 9% and 20%, respectively. Sixty-seven percent of the patients had relapse/progressive disease after follow-up. In conclusion, the clinical features as well as the outcomes of Thai patients with MCL were comparable to patients in Western countries. Newly diagnosed patients should be treated with novel modalities other than conventional CHOP chemotherapy in order to improve the outcomes.

Keywords: *Mantle Cell Lymphoma, Thai*

J Med Assoc Thai 2004; 87(9): 1071-5

Mantle cell lymphoma (MCL) is a disease entity recently incorporated in the Revised European American Lymphoma (REAL) and the World Health Organization (WHO) classifications of lymphoid neoplasms[1,2]. In the old terminology, the disease was referred to as small cleaved cell lymphoma under the Working Formulation and centrocytic lymphoma by the Kiel classification[3,4]. In the analysis for the relative distribution of lymphoma subtypes based on the REAL classification, the International Lymphoma Project Study Group reported the frequency of 3-4% for MCL[5]. Among the 221 newly diagnosed Thai patients with non-Hodgkin's lymphoma, Intragumtornchai et al found the incidence of 4.4% for MCL[6]. Albeit histologically appearing as a small cell variant, MCL has a more aggressive disease course and poor prognosis compared with other lymphomas of small lymphocytes [7,8]. The purpose of this study was to determine the clinical features as well as the therapeutic outcomes of Thai patients diagnosed as MCL treated at a tertiary medical center and to compare the data with those reported from a Western population.

Correspondence to : Intragumtornchai T, Division of Hematology, Department of Medicine, King Chulalongkorn Memorial Hospital, Rama IV Rd, Bangkok 10330, Thailand. Phone: 0-2256-4564, Fax: 0-2253-9466, E-mail: itanin@netserv.chula.ac.th

Patients and Method

A retrospective analysis on clinical and pathological data on patients aged ≥ 15 years newly diagnosed with MCL from January 1997 to December 2002 at King Chulalongkorn Memorial Hospital were conducted. The diagnosis of MCL was confirmed by pathology review by one member of the Hemato-pathology Department, King Chulalongkorn Memorial Hospital (PW). The diagnostic criteria for MCL were consistent histopathologic and/or immunophenotypic features (CD20+, CD5+, CD23- and cyclin D1+) as

defined by the REAL classification[1]. Clinical data obtained on each patient included age at diagnosis, sex, performance status (PS) (ECOG grade 0-4), B symptoms (fever >38.5^{0}C or weight loss >10% in the previous six months or night sweats), sites of diseases, Ann Arbor stage (I-IV), presence of bulky disease (> 10 cm diameter), number of extranodal disease, iliac crest bone marrow aspiration and biopsy, chest radiography, abdominal and pelvic computed tomography, serum lactate dehydrogenase (LDH), risk group according to the international prognostic index (IPI)[9], complete blood count and peripheral blood smear, renal and liver function tests and regimen of chemotherapy treatments. Outcomes were assessed as tumor response (complete remission [CR], partial remission [PR], stable disease [SD] and progressive disease [PD]) and the rates of long-term survivals (overall survival [OS], progression-free survival [PFS] and disease-free survival [DFS]).

CR was defined as disappearance of all measurable or evaluable diseases, signs or symptoms related to the tumor for at least 4 weeks. PR was defined as a greater than 50% reduction in the sum of the product of two perpendicular diameters of all measurable lesions, compared with pretreatment measurements. PD was an increase in the product of two perpendicular diameters of a measured lesion by $\geq$ 25% over the size present at entry or for patients who responded, the size at the time of maximum regression and/or the appearance of new areas of malignant disease. Patients who did not meet any of the preceding definitions were classified as SD. OS duration was calculated from the date of diagnosis to the date of death or last follow-up evaluation. PFS was measured from the date of diagnosis to the date of PD, relapse (in patients with CR), death from any event or last follow-up evaluation. DFS was applied only to patients who obtained CR; the duration was measured from the date of CR to the date of relapse or last follow-up evaluation. Survival curves were estimated by the actuarial method of Kaplan-Meier and were compared using the log-rank test. Comparison of the variables between the two groups were made using the Fisher-exact test. All tests of significance were two-sided with alpha value $\leq$ 0.05.

Results

Patient characteristics

A total of 21 patients were eligible. The median age of the patients was 54 years (range, 38-79) (Table 1). Male had preponderance to female (ratio 4:1). Generalized lymphadenopathy was the most frequent physical finding. Hepatosplenomegaly was found in one-third of the patients. One patient presented with predominant splenomegaly without lymphadenopathy. Eight patients had gastrointestinal involvement (6, gastric, 2, small intestine and 2 cecum); 2 of these had multiple site involvement. Five patients had Waldeyer's ring involvement, in whom 4 had concurrent gastrointestinal lesions. Most patients had advanced disease (stage III, IV). Bone marrow involvement was found in 52% of the patients. Elevated serum LDH was found in 65% of the patients and 56% belonged to the high- and high-intermediate risk group by the IPI.

Table 1. Comparison of clinical features between Thai and Caucasian patients with mantle cell lymphoma

	Current Study*		Weisenburger et al[11]
	N	%	%
Age (median)(year)	54 (range, 38-79)		60
Male : female	4:1		4:1
Generalized lymphadenopathy	14	67	90
Gastrointestinal involvement	7	33	30
Hepatomegaly	7	33	60
Splenomegaly	8	38	20
Waldeyer's ring involvement	5	24	10
Stage III, IV	18	85	90
B symptoms	11	53	40
Poor performance status (ECOG score >1)	7	33	20
Bulky disease	2	9	30
Bone marrow involvement	11	52	80
Elevated serum LDH	12	67**	40
IPI, high and HI	10	56**	NA

* N = 21, ** N = 18

Abbreviation: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, international prognostic index; HI, high-intermediate

On admission, fifty-two percent of the patients had a hemoglobin value < 12 g/dl (Table 2). Five patients had white blood cell count > 12 x 10^9/l (range, 14.3-110); all of them had absolute lymphocytosis (median 20.2 x 10^9/l, range, 13.2-82.5) and circulating lymphoma cells (median 74%, range, 52-93). Total birilubin > 2 mg/dl (11.3 mg/dl) was found in 1 patient. Thirty-one percent of the patients had serum albumin level < 3.5 g/dl.

Outcomes

Seventy-six percent of the patients were treated with CHOP (vincristine, cyclophosphamide, doxorubicin, prednisolone) or CVP (vincristine, cyclophosphamide, prednisolone) regimen. One patient each was treated with the corporate regimen of Rituximab/CHOP/ESHAP (etoposide, solumedrol, high-dose ara-C, platinol) and Hyper-CVAD/MA (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, high-dose ara-C), respectively. Two patients were referred to other hospitals and one patient expired before constituting treatment. Fifty-nine percent of the patients achieved CR and two patients had PD during induction chemotherapy (Table 3). With a median follow-up time of 13 months (range, 1-62 months), the rates of 3-year OS, PFS and DFS were 32%, 9% and 20%, respectively. Sixty-seven percent of patients had PD after induction therapy. For patients who were treated with CHOP, the CR rate was 64%; the rates of OS and PFS were 33% and 11%, respectively, none remained disease-free at year 3.

Discussion

MCL is one of the lymphomas with a grave prognosis. The disease corporates the worst characteristics of low-grade and high-grade lymphomas, ie, incurable but aggressive clinical course. The present study showed that the median survival of the patients was only 34 months. Even in patients with disease remission, 70% of them relapsed after follow-up. The long-term survival of patients in the present series was inferior to patients with other types of B-cell lymphomas but comparable to patients with peripheral

Table 2. Laboratory Features

	Median	Range
Hemoglobin (g/dl)	11.9	6.6-14.3
White blood cell count (x 10^9/l)	6.9	2.7-110
Platelet count (x 10^9/l)	210	11-645
Absolute lymphocyte count (x 10^9/l)	1.8	0.8-82.5
Serum albumin (g/dl)	3.9	2.4-5.3

Table 3. Outcomes of treatment

Complete remission	59%
Partial remission	12%
Progressive disease	78%
Relapse	70%

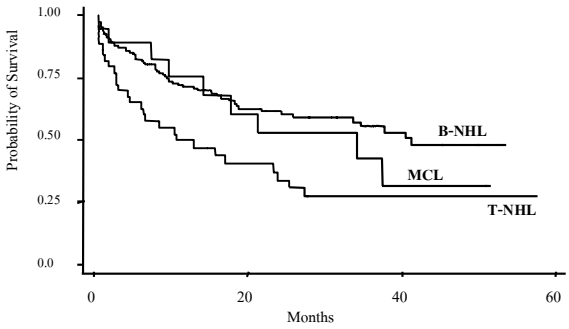

Fig. 1 Comparison of the overall survival curves of patients with mantle cell lymphoma (MCL)(current study) and patients with B-cell (B-NHL) and T-cell lymphomas (T-NHL) treated at King Chulalongkorn Memorial Hospital [10]

T-cell lymphomas treated at the same time period in our institution[10] (Fig 1).

The present study revealed that the clinical features of MCL in Thai patients were generally similar to patients described in Western countries[11] (Table 1). There was a male preponderance in both races; however, the median age of Thai patients was less than the Western population. Generalized lymphadenopathy with advanced disease (stage III, IV) was the main presenting feature in both groups of patients. One-third of the patients had circulating lymphoma cells and more than half had bone marrow involvement at diagnosis. Regarding gastrointestinal involvement, gastric ulcer was the most frequent abnormality found in Thai patients. It is notable that the characteristic multiple lymphomatous polyposis which was reported in 20% of Western population was not demonstrated in patients in the present report[12]. This might be due to the small number of patients in the present series. Waldeyer's ring involvement was also found more frequently in Thai patients. The present study showed that more than half of the patients belonged to the high- and high-intermediate risk according to the IPI.

The present study showed that the median survival of the patients was 34 months and the 5-year OS was 32% (95% confidence interval, 10-56%). This is in accordance with the median survival of 3 and 4 years as reported from a number of large series of the analysis of patients with MCL[11,13,14]. It is notable that patients with a nodular pattern in general had a significantly longer survival (77 to 88 months) when compared to those with diffuse MCL (30-33 months)[11,15]. Meusers et al, in a randomized multicenter trial, found that the anthracycline-based

chemotherapy did not improve the outcome compared to CVP[116]. Patients treated with CHOP in the present series obtained comparable rates of OS (33% vs 25%, P = 0.58) compared to those treated with CVP.

Recently, investigators showed that newer therapies might improve the outcomes of patients with MCL. In 1994, Khouri et al treated 25 newly diagnosed patients with hyper-CVAD/MA followed by high-dose therapy and autologous or allogeneic stem cell transplantation[17]. Rates of CR and PR of 38% and 55% were achieved after the first four courses of induction chemotherapy. The OS and EFS at 3 years were 92% and 72% respectively. Romaguera et al treated 94 patients with rituximab in combination with hyper-CVAD/MA[18]. The rate of CR was 89% and OS at 3 years was 81%. Recently, Dreyling et al reported a CR rate of 33% and the OS rate of 62% in 24 patients with relapsed MCL treated with rituximab plus FCM (fludarabine, cyclophosphamide, mitoxanthrone)[19].

In conclusion, the present study revealed that the clinical features as well as the outcomes of Thai patients with MCL were comparable to patients in Western countries. The most common presenting feature was generalized lymphadenopathy with advanced disease. With conventional chemotherapy, the long-term OS was only 32% and the majority of patients relapsed or had PD after follow-up. To improve the outcomes, newly diagnosed patients should be treated with novel modalities other than conventional CHOP chemotherapy.

References

1. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994; 84: 1361-92.
2. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol 2000; 18: 2788-9.
3. Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute-sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a Working Formulation for Clinical Usage. Cancer 1982; 49: 2112-35.
4. Lennert K, Stein H, Kaiserling E. Cytological and functional criteria for the classification of malignant lymphomata. Br J Cancer 1975; 31(Suppl 2): 29-43.
5. The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the Non-Hodgkin's Lymphoma Sudy Group classification of non-Hodgkin's lymphoma. Blood 1997; 89: 3909-18.
6. Intragumtornchai T, Wannakrairoj P, Sutcharitchan P, Swasdikul D. Non-Hodgkin's lymphoma in Thai Patients according to the Revised European American Classification. Asian Pac J Allergy Immunol 1999; 17(Supply1): 28(Abstract).
7. Agatoff LH, Connors JM, Klasa RJ, et al. Mantle cell lymphoma; a clinicopathologic study of 80 cases. Blood 1997; 89: 2067-78.
8. Fisher RI. Mantle-cell lymphoma: classification and therapeutic implications. Ann Oncol 1996; 7(Suppl 6): S35-9.
9. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model of aggressive non-Hodgkin's Lymphoma. N Engl J Med 1993; 329: 987-94.
10. Intragumtornchai T, Rojnuckarin P, Sutcharitchan P, Wannakrairot P. Prognostic significance of the immunophenotype versus the international prognostic index in aggressive non-Hodgkin's lymphoma. Clin Lymphoma 2003; 4: 52-5.
11. Weisenburger DD, Armitage JO. Mantle cell lymphoma : an entity comes of age. Blood 1996; 87: 4483-94.
12. O'Brian DS, Kennedy MJ, Daley PA, et al. Multiple lymphomatous polyposis of the gastrointestinal tract: a clinicopathologically distinctive form of non-Hodgkin's of B-cell centrocytic type. Am J Surg Pathol 1989; 13: 691-99.
13. Zucca E, Roggero E, Pinotti G, et al. Patterns of survival in mantle cell lymphoma. Ann Oncol 1995; 6: 259-62.
14. Bosch F, Lopez-Guillermo A, Campo E, et al. Mantle cell lymphoma: presenting features, response to therapy, and prognostic factors. Cancer 1998; 82: 567-75.
15. Lardelli P, Bookman MA, Sundeen J, Longo DL, Jaffe ES. Lymphocytic lymphoma of intermediate differentiation. Morphologic and immunophenotypic spectrum and clinical correlations. Am J Surg Pathol 1990; 14: 752-63.
16. Meusers P, Engelhard M, Bartels H, et al. Multicentre randomized therapeutic trial for advanced centrocytic lymphoma. Anthracycline does not improve prognosis. Hematol Oncol 1989; 7: 365-80.
17. Khouri IF, Romaguera J, Kantarjian H, et al. Hyper-CVAD and high-dose methotrexate/cytarabine followed by stem-cell transplantation: an active regimen for aggressive mantle-cell lymphoma. J Clin Oncol 1998; 16: 3803-9.
18. Romaguera J, Cabanillas N, Dang N, et al. Mantle cell lymphoma: update on results after R-HCVAD without stem cell transplant. Ann Oncol 2002; 13(Suppl 2): 8 (Abstract).
19. Dreyling MH, Forstpointner R, Repp R, et al. Combined immuno-chemotherapy results in superior remission and survival rates in recurrent follicular and mantle cell lymphoma: final results of a prospective randomized trial of the GLSG. Hematol J 2003; 4(Suppl 2): 150 (Abstract).

แมนเติลเซลล์ลิมโฟมาในผู้ป่วยไทย

ธานินทร์ อินทรกำธรชัย, พลภัทร โรจน์นครินทร์, ปราณี สุจริตจันทร์, พงษ์ศักดิ์ วรรณไกรโรจน์

Mantle cell lymphoma (MCL) เป็นโรคซึ่งถูกบรรจุไว้ในระบบการจัดแบ่งโรคของลิมโฟมาชนิดใหม่ ลักษณะทางคลินิกรวมทั้งผลการรักษาในผู้ป่วยไทยยังไม่เคยมีผู้รายงานไว้ ผู้รายงานศึกษาแบบย้อนหลังในผู้ป่วยใหม่ซึ่งได้รับการวินิจฉัย MCL ที่โรงพยาบาลจุฬาลงกรณ์ระหว่างเดือนมกราคม 2540 ถึงเดือนธันวาคม 2545 พบมีผู้ป่วย 21 ราย อายุเฉลี่ยเท่ากับ 54 ปี (พิสัย, 38-79) อัตราส่วนของชาย:หญิงเท่ากับ 4:1 อาการสำคัญที่พบบ่อยที่สุดเมื่อแรกวินิจฉัยได้คือมีต่อมน้ำเหลืองโตทั่วตัว ผู้ป่วยร้อยละ 80 อยู่ในระยะที่ III, IV (ระบบ Ann Abor) ร้อยละ 56 อยู่ในกลุ่มเสี่ยงสูงและสูงปานกลางตามเกณฑ์ของ international prognostic index ผู้ป่วยส่วนใหญ่ได้รับการรักษาด้วย CHOP (vincristine, cyclophosphamide, doxorubicin, prednisolone) หรือ CVP (vincristine, cyclophosphamide, prednisolone) พบมีอัตรา complete remission เท่ากับ 59% ภายหลังติดตามนานเฉลี่ย 13 เดือน (พิสัย, 1-62 เดือน) อัตราการมีชีวิตโดยรวม, โดยปราศจากโรคกำเริบและโดยปราศจากโรคเท่ากับ 32%, 9% และ 20% ตามลำดับ ร้อยละ 67 มีโรคกลับ/กำเริบหลังติดตาม โดยสรุปลักษณะทางคลินิกรวมทั้งผลการรักษาผู้ป่วยไทยไม่ต่างจากผู้ป่วยตะวันตก ผลการรักษาด้วย CHOP ได้ผลไม่ดี ควรหาวิธีการรักษาใหม่ที่ได้ผลดีกว่า