Clinico-pathologic Profile and Clinical Outcomes of Patients with Indolent Lymphoma at the Cancer Institute of the Philippine General Hospital: A Seven-year Experience

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Abstract

Introduction: Indolent lymphoma (IL) is a slowly growing lymphoma, generally refractory to conventional chemotherapy. There are several types of IL, which includes follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), and waldenstrom macroglobulinemia/ lymphoplasmacytic lymphoma (WM/LPL). Presently, there are no known data in the Philippines on IL. This study is done to determine the clinico-pathologic profile and outcomes of Filipino patients with IL.

Methods: This study is a retrospective chart review of outpatient department cases of IL seen at the Philippine General Hospital-Cancer Institute from January 2009 to January 2016. The following were documented: age; gender; primary location; presence or absence of B symptoms; type of IL; Ann-arbor stage; prognostic indices for FL and MCL; and staging with bone marrow aspiration and whole body CT scan. Treatment intervention and clinical outcomes were documented.

Results: This study showed that SLL was the most common IL. Most were elderly (>40 years old); male; lacked B symptoms; limited disease; and primary location at or near the orbital area. MCL were seen in all risk groups. Follicular lymphoma (FL) were mostly low risk and had grade one histology. Majority had disease control regardless of treatment intervention. Most patients with recurrence/progression after initial treatment had limited disease but were understaged. Most of the patients were not staged with bone marrow aspiration or whole body computed tomography.

Conclusion: The results of this study are mostly consistent with known literature on IL. Absence of B symptoms and limited disease may indicate a low-grade histology. Observation was the most common option for asymptomatic patients.

Keywords: indolent, lymphoma, Philippines

Introduction

Indolent non-hodgkin's lymphomas (NHL) were made up of mature B cells with a long median survival and generally poor response to conventional chemotherapy.[1] Some reports included T-cell large granular lymphocyte leukemia.[2] Because of its chronic course and mostly asymptomatic nature, prognosis was relatively good.[3]

Bone marrow involvement was common. As a result, guidelines included bone marrow aspiration (BMA) as an essential or useful component in diagnosing and staging indolent lymphoma (IL). Presently, there is no established treatment of choice for IL. Most guidelines recommends observation for asymptomatic patients. Treatment may be given once the patient becomes symptomatic. The goal for treatment was to maintain the best quality of life. Alteration of this approach needed evidence of survival benefit with early therapy. Options for management depended on whether the lymphoma was advanced or localized. Generally, management options included the "watch and wait approach", radiotherapy, chemoimmunotherapy, autologous/allogenic stem cell transplantation, radioimmunotherapy and monotherapy with monoclonal antibodies.[4]

Several classification schemes had been developed for NHL. The initial classification scheme by the International Panel Working Formulation of the National Cancer Institute included three morphologically different groups. Eventually, various molecular and immunohistochemistry tests were discovered, which further improved the classification of NHL. The present staging for NHL was an amalgamation of these advances in technology - the 2008 REAL/WHO 2008 Classification. In the present classification scheme, IL was not considered a unique group; it was divided based on its morphology, phenotype, genotype and clinical findings.[5] Histologically, IL was made up of small to medium-sized cell, however further characterization with immunohistochemistry and/or chromosomal analysis was required.[3]

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Among IL, follicular lymphoma (FL) was the most common subtype and the second most common NHL after diffuse large B cell lymphoma (DLBCL) in America and Europe.[5] FL was composed of malignant germinal center-derived B-cells that exhibited follicular growth pattern. The genetic hallmark was t(14;18), which led to ectopic expression of the Bcl2, an anti-apoptotic protein.[6] WHO divided FL into three grades based on the presence of centroblasts and/or centrocytes. Grade one and two were managed similarly while grade three was managed like DLBCL.[7,8] The immunophenotype of FL was usually positive for pan-B cell markers (CD20), specific germinal center B-cell markers (Bcl6 and CD10) and Bcl2. Occasional cases may be negative for CD10 or Bcl2. There were conflicting reports on the prognostic significance of Bcl2.[9]

Small lymphocytic lymphoma (SLL) consisted of abnormal lymphocytes found primarily in the lymph nodes and bone marrow. Typical immunophenotype included CD23 positive, CD5 positive, and cyclin D1 negative tumor. A diagnosis of SLL should only be made when effacement of lymph node architecture was seen. Additional diagnostics included determination of the certain deletions (del13q, del11q, del17p) that were important prognostic and/or predictive factors. In contrast, chronic lymphocytic leukemia (CLL) consisted of abnormal lymphocytes in the bone marrow and blood.[5]

Mantle cell lymphoma (MCL) had the characteristics of an indolent disease and an aggressive lymphoma. Similar to an indolent disease, it generally didn't respond well to conventional chemotherapy. It was associated with t(11;14). Most MCL were positive for the cyclin D1 protein, however some cases were negative for cyclin D1. Clinically, there was no difference between a cyclin D1-positive and a cyclin D1-negative MCL.[10] However, cyclin D1 status was an independent factor for survival.[11] Since this lymphoma could occur in the gastro-intestinal (GI) tract, EGD and colonoscopy should be done to confirm Ann-arbor stage.[8]

Marginal zone lymphoma (MZL) based on the REAL/WHO 2008 classification was divided into nodal, extranodal and splenic subtypes. The marginal zone corresponded to the outer part of secondary follicles. It was well formed in the spleen, intra-abdominal lymph nodes and musoca-associated lymphoid tissue (MALT). The most common location of extranodal MZL was the stomach, associated with t(11;18). The presence of this translocation was predictive of poor response to anti-Helicobacter pylori regimen. MZL was strongly positive for IgM, IgG or IgA.[5]

Waldenstrom's macroglobulinemia(WM) was normally characterized by bone marrow infiltration of lymphoplasmacytic cells and IgM monoclonal gammopathy in the serum. It was both a pathologic and a clinical diagnosis. Lymphoplasmacytic differentiation was not pathognomonic for WM, because it could also be seen in splenic MZL. Clinically, it may present with symptoms of hyperviscosity. Morphologically, intranuclear (Dutcher bodies) and intracytoplasmic (Russell bodies) inclusions were usually noted.[12]

Presently, there were no known local studies on IL. For this reason, the purpose of this study was to determine the baseline clinical and pathologic characteristics of patients with IL seen at the Philippine General Hospital-Cancer Institute (PGH-CI). Obtaining real-world data in the Philippines was important because it could be used to plan future health-care services and monitor the impact of therapeutic changes.[13]

Methods

A retrospective review of the out-patient department (OPD) charts of patients with IL seen at the PGH-CI was done. It only included patients diagnosed with B-cell Non-Hodgkin's lymphoma. This included FL, MCL, MZL (gastric MALtoma, non-gastric MALtoma,nodal,splenic), SLL and WM/LPL. The presence of lymphoplasmacytic differentiation on bone marrow and serum IgM monoclonal gammopathy was used to diagnose WM. On the other hand, this study did not include patients at the charity ward, pay ward or intensive care unit. It also did not include patients diagnosed purely with leukemia.

This study included patients diagnosed as IL morphologically and confirmed through immunohistochemistry seen at the PGH-CI from January 2009 to January 2016.

Data was collected using an encoded data collection form. Histopathologic records of cases of IL were retrieved and reviewed from the PGH Department of Laboratories. The following data were documented from review of hospital charts as part of the clinical and pathologic profile:

- Age
- Gender
- Presence or absence of B symptoms
- Primary site of lymphoma
- Staging with BMA or whole body CT scan
- Type of IL
- Ann-arbor stage
- Prognostic indices (MIPI for MCL and FLIPI for FL)
- Grading for FL (grade one, two, or three)

The type of treatment intervention was also documented, which included surgery, radiotherapy, chemotherapy with or without immunotherapy, or combined modality therapy. Patients who did not follow-up after the planned treatment intervention were also documented. For the patients who underwent chemotherapy with or without immunotherapy, the type of regimen, number of cycles, and clinical

outcomes (complete response, partial response, stable disease, progression, recurrence) after treatment were documented. For the patients who underwent radiotherapy, they were stratified into three different dose range based on the most commonly used radiotherapy dose for IL - <24 Gy, 24-30 Gy, and >30 Gy. Clinical outcomes after radiotherapy were documented. For those who underwent surgery, outcomes were classified as complete or partial resection. After the surgery, the patients were followed-up and were noted if it the disease progressed, recurred, or remained stable. The month when the clinical outcome occurred was documented. For the patients who did not receive any intervention, the disease was observed if it progressed, recurred or remained stable. The month when the clinical outcome occurred was documented. For the patients who underwent combined modality therapy, they were classified if they received surgery then chemotherapy; chemotherapy then surgery; or chemotherapy then radiotherapy. Clinical outcomes and the month when this occurred were documented.

Descriptive statistics was used to summarize the clinical profile, pathologic profile, and treatment outcomes. Definition of the clinical outcomes was based on the original International Working Group criteria[5] for response assessment for NHL.

The protocol was submitted for review to the Technical Review Board (TRB). After it was approved by the TRB, it was passed to the University of the Philippines Manila Research and Ethics Board (UPMREB). The study was conducted with the approval of the UPMREB. Since this was a retrospective review, there was no direct contact between the investigator and the patient. Confidentiality was ensured by assigning a patient a code number associated with his/her case number to preserve anonymity. The study was funded by the investigators. There were no conflicts of interest.

Results

A total of 32 patients were included in this study. Of the 32 patients, three had MCL; ten had MZL; 12 had SLL; and seven had FL. No patient with WM/LPL was included in the study. There were two cases of thyroid lymphoma both with a MZL subtype. There were five cases of GI lymphoma (three MZL and two SLL). Treatment interventions were any of the following: chemotherapy, surgery, combined modality therapy or no active intervention.

More than eighty percent (>80%) of patients with IL were above 40 years old (Table I). The eldest patient was 74 years old, diagnosed with FL; the youngest 27 years old, diagnosed with SLL. Majority were male with predominantly SLL and MZL histology (Table II). Most presented with B symptoms (Table III). Most were located in the orbital, cervical and inguinal area (Table IV). Most were not staged with BMA, except for some patients with SLL (Table V). CT scan of the primary site was done for all patients but most were staged with chest xray and/or with holoabdominal ultrasound only. (Table VI). Majority had limited stage except for MCL (Table VII).

There were three patients with MCL. One had low, intermediate, and high risk MIPI. Most patients with FL had low or intermediate risk FLIPI and grade one histology (Table VIII).

Table I. Frequency of indolent lymphoma based on age

Age Range *Frequency (%)*	Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
20-29	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (3.1)
30-39	0 (0)	1 (10)	2 (16.7)	1 (14.3)	4 (12.5)
40-49	1 (33.3)	3 (30)	3 (25)	1 (14.3)	8 (25)
50-59	0 (0)	3 (30)	3 (25)	3 (42.8)	9 (28.1)
60-69	1 (33.3)	3 (30)	3 (25)	0 (0)	7 (21.9)
≥70	1 (33.3)	0 (0)	0 (0)	2 (28.6)	3 (9.4)
Total	3 (100)	10 (100)	12 (100)	7 (100)	32 (100)

Table II. Frequency of indolent lymphoma based on gender

Gender *Frequency (%)*	Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
Male	1 (33.3)	6 (60)	8 (66.7)	3 (42.9)	18 (56.3)
Female	2 (66.7)	4 (40)	4 (33.3)	4 (57.1)	14 (43.7)
Total	3 (100)	10 (100)	12 (100)	7 (100)	32 (100)

Table III. Frequency of indolent lymphoma based on B symptoms

B Symptoms *Frequency (%)*	Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
Present	2 (66.7)	0 (0)	4 (33.3)	3 (42.9)	9 (28.1)
Absent	1 (33.3)	10 (100)	8 (66.7)	4 (57.1)	23 (71.9)
Total	3 (100)	10 (100	12 (100)	7 (100)	32 (100)

Table IV. Frequency of indolent lymphoma based on location

Primary Location *Frequency (%)*	Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
Eye/Orbit/ Conjunctivae	1 (33.3)	5 (50)	1 (8.3)	0 (0)	7 (21.9)
Tonsillar	0 (0)	0 (0)	0 (0)	1 (14.3)	1 (3.1)
Sub-mandibular	2 (66.7)	0 (0)	0 (0)	0 (0)	2 (6.3)
Maxillary	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (3.1)
Cervical	0 (0)	0 (0)	4 (33.4)	2 (28.6)	6 (18.8)
Thyroid	0 (0)	2 (20)	0 (0)	0 (0)	2 (6.3)
Axillary	0 (0)	0 (0)	2 (16.8)	0 (0)	2 (6.3)
Gastric	0 (0)	1 (10)	0 (0)	0 (0)	1 (3.1)
Pancreas	0 (0)	0 (0)	0 (0)	1 (14.3)	1 (3.1)
Colon	0 (0)	2 (20)	1 (8.3)	0 (0)	3 (9.4)
Ileocecal	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (3.1)
Abdominal area	0 (0)	0 (0)	1 (8.3)	0 (0)	1 (3.1)
Inguinal	0 (0)	0 (0)	1 (8.3)	3 (42.8)	4 (12.4)
Total	3 (100)	10 (100)	12 (100)	7 (100)	32 (100)

Table V. Frequency of indolent lymphoma based on staging with BMA

BMA Done *Frequency (%)*	Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
Yes	0 (0)	0 (0)	3 (25)	0 (0)	3 (9.4)
No	3 (100)	10 (100)	9 (75)	7 (100)	29 (90.6)
Total	3 (100)	10 (100)	12 (100)	7 (100)	32 (100)

Table VI. Frequency of indolent lymphoma based on staging with CT scan

Whole Body CT Scan *Frequency (%)*	Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
Yes	2 (66.7)	1 (10)	5 (41.7)	2 (28.6)	10 (31.2)
No	1 (33.3)	9 (90)	7 (58.3)	5 (71.4)	22 (68.8)
Total	3 (100)	10 (100)	12 (100)	7 (100)	32 (100)

Table VII. Frequency of indolent lymphoma based on Ann-arbor stage

Ann-arbor Stage *Frequency (%)*		Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
Limited	I	0 (0)	9 (90)	6 (50)	2 (28.6)	17 (53.1)
	II	1 (33.3)	1 (10)	2 (16.7)	2 (28.6)	6 (18.8)
Advanced	III	2 (66.7)	0 (0)	3 (25)	2 (28.6)	7 (21.9)
	IV	0 (0)	0 (0)	1 (8.3)	1 (14.2)	2 (6.2)
Total		3 (100)	10 (100)	12 (100)	7 (100)	32 (100)

Table VIII. Frequency of follicular lymphoma based on flipi and grade

Pathologic Characteristic	Category	Frequency (%)
Follicular Lymphoma International Prognostic Index (FLIPI)	Low risk	3 (42.9)
	Intermediate risk	3 (42.9)
	High risk	1 (14.2)
	Grade one	3 (42.8)
	Grade two	2 (28.6)
	Grade three	2 (28.6)

FLIPI 0-1: Low risk FLIPI 2: Intermediate risk FLIPI 3-4: High risk

Table IX. Outcomes of indolent lymphoma after chemotherapy ± targeted therapy

Chemotherapy ± Targeted Therapy *Frequency (%)*	Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
Complete Response	0 (0)	1 CHOPx6 (50)	1 CHOPx6 (16.7)	0 (0)	2 CHOPx6 (15.3)
Partial Response	2 CHOPx8 R-CHOPx8 (100)	1 CHOPx6 (50)	2 CHOPx6 CHOPx4 (33.3)	1 CHOPx5 (33.3)	6 CHOPx4, CHOPx5, CHOPx6, CHOPx8, R-CHOPx8 (46.2)
Stable Disease	0 (0)	0 (0)	1 CHOPx6 (16.7)	0 (0)	1 CHOPx6 (7.7)
Progression	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Did not follow-up	0 (0)	0 (0)	2 (33.3)	2 (66.7)	4 (30.8)
Total	2 (100)	2 (100)	6 (100)	3 (100)	13 (100)

Table X. Outcomes of indolent lymphoma with no active intervention

Observation	Mantle Cell	Marginal Zone	Small Lymphocytic	Follicular	Total
Stable	1 (100) 8 mos.	0 (0)	0 (0)	1 (50) 24 mos.	2 (25) 8 mos. 24 mos.
Progression	0 (0)	1 (50) 24 mos.	0 (0)	0 (0)	1 (12.5) 24 mos.
Did not follow-up	0 (0)	1 (50)	3 (100)	1 (50)	5 (62.5)
Total	1 (100)	2 (100)	3 (100)	2 (100)	8 (100)

Chemotherapy with or without targeted therapy was the most common management. Most of the patients had partial response to chemotherapy. Regimens used were CHOP or R-CHOP (four to eight cycles). All patients who completed chemotherapy had disease control, although a substantial number did not follow up (Table IX).

Some patients did not receive any active intervention. These patients were observed clinically and through imaging. Majority were lost to follow-up. For patients who followed up, two had stable disease and one progressed 24 months after initial diagnosis (Table X). On the other hand, most patients who had surgery had complete resection, especially for GI lymphoma. For those who followed up after resection, half had disease control (Table XI).

Half of the patients who had combined modality therapy (chemotherapy and radiotherapy) were diagnosed with FL had complete response (Table XII).

Discussion

Clinical Profile

Indolent lymphoma (IL) belonged to a heterogenous group of low-grade B cell Non-hodgkin's lymphoma.[1] This study showed that the most common IL in the PGH-CI was SLL followed by MZL, FL, and MCL. SLL and CLL were manifestations of the same disease but the former should have a tissue diagnosis. The frequency of SLL may be underestimated in this study because CLL, the leukemic variant, was not included. Compared to other countries, FL was the most common histology.[14]

In this study, majority of MZL were non-gastric, mostly in the eyelid. There was one case of gastric MZL. Gastric MZL should ideally be tested for t(11;18) and Helicobacter pylori. These tests were not done. After one consult, the patient was lost to follow-up. Hepatitis C should ideally be tested for all patients with MZL, also not done.[8]

Table XI. Outcomes of indolent lymphoma based on resection status

Surgery	Marginal Zone Lymphoma (Total number=5)				Small Lymphocytic Lymphoma (Total number=2)				Total (n=7)
	Recurrence	Progression	Stable Disease	Did not follow-up	Recurrence	Progression	Stable Disease	Did not follow-up	Recurrence = R Progression = P Stable Disease = SD Did not ff-up = DNF
Complete Resection	1 (7 mos)	0	1 (2 mos)	2	0	0	0	1	MZL, R=1 (7 mos) MZL, SD=1 (2 mos) DNF=3
Partial Resection	0	0	1 (6 mos)	0	0	1 (9 mos)	0	0	MZL, SD=1 (6 mos) SLL, P=1 (9 mos)
Total	1	0	2	2	0	1	0	1	R=1 (7 mos) SD=2 (2 mos, 9 mos) P=1 (9 mos) DNF=3

Table XII. Outcomes of indolent lymphoma after combined modality therapy

Combined Modality	Marginal Zone Lymphoma	Small Lymphocytic Lymphoma	Follicular Lymphoma
Surgery → chemotherapy	1 (Partial response after chemotherapy)	0	0
Chemotherapy → surgery	0	1 (Partial response after chemotherapy)	0
Chemotherapy → RT (R-CHOPx8 then LINAC 30Gy R-CHOPx3 then LINAC 30.6 Gy)	0	0	2 (Complete response after RT)

Only a handful of cases were included in this study. Possible reasons may be due to misdiagnosis or poor health seeking behavior. Misdiagnosis may be due to poor specimen handling; poor tissue processing; and lack of a more comprehensive training in hematopathology.[14] Possible reasons for poor health seeking behavior especially for developing countries included low educational attainment; lower priority on health policies by the government; and certain Filipino traits such as procrastination.[15,16]

Diffuse large B cell lymphoma (DLBL) was the most common NHL in adults. It could also co-exist with IL. DLBCL could also arise from IL in a process called histologic transformation. Histologic transformation could be monitored by checking for presence of rapidly growing masses, extranodal disease, new-onset B symptoms, hypercalcemia, and elevated LDH.[5] Patients with mixed IL and DLBCL should be managed aggressively with chemotherapy.[8] One case with FL in histologic transformation received chemotherapy.

Indolent lymphoma (IL) was mostly seen in elderly males, as shown in this study. In developed countries, most IL occurred in the elderly, usually those in their 60's or 70's.[14] The predominance of male diagnosed with lymphoma may be due to less access to medical care for women in developing countries.[14] Indolent lymphoma (IL) was usually asymptomatic, in contrast to DLBCL.[17] This may suggest that patients with B symptoms have a more aggressive histology.

The most common location of the mass in the study was at or near the orbital area. Most orbital mass in the study were MZL similar to a study done in Germany.[18] A study done in the United States several decades before showed most presented with lymphadenopathy and fever.[20] The difference observed may be due to change in the disease landscape over the years.

Most IL in this study had Ann-arbor stage I and II. A study in Pakistan of extranodal DLBCL mostly presented with advanced stage.[17] Most IL with a limited stage may be due to a slow glowing biology. In contrast to other IL, MCL could be indolent or aggressive. A study in Europe showed that majority of patients with MCL had advanced stage.[20] This may be due to a more aggressive bone marrow invasion.

Staging for IL included BMA and whole body CT scan recommended as standard of care.[8] Most of the cases in this study were understaged. Staging would affect treatment and prognosis, hence it should be always be accurate. The authors hypothesized that understaging may be due to lack of knowledge on the need for BMA for accurate staging; lack of skilled doctors to perform BMA; and lack of money by the patient for BMA (including immunophenotyping) and whole body CT scan. However, these were only assumptions and would need further validation.

In 2014, PET-CT scan was included in staging and response assessment of NHL referred to as Lugano criteria.[8] PET scan was based on the idea that metabolically active cells take up the labeled glucose (FDG) to be used for its various cellular processes.[5] Cells who took the labeled glucose were then detected. However, the Lugano criteria was limited only to cells with active FDG uptake or aggressive lymphomas. In addition, this criteria was only validated for DLBCL and Hodgkin's lymphoma[8] The original International Working Group criteria (IWG 1999) could be used for IL which used CT scan only.[8] In addition, PET-CT scan was not typically done on patients of PGH diagnosed with IL during the study period due to economic constraints. In this study, one case of FL grade three was staged with whole body PET/CT scan. Studies showed that FL grade three behaved similarly to aggressive lymphomas.[5,8] Guidelines indicated that FL grade three should be treated similarly to DLBCL.

Pathologic Profile

Prognostic indices were developed to guide patient counseling and treatment decisions.[5] Several prognostic indices were validated for NHL. The International Prognostic Index (IPI) was used for DLBCL consisting of age, stage, performance status, extranodal involvement and LDH. For IL, FL Internal Prognostic Index (FLIPI) and Mantle cell International Prognostic Index (MIPI) were used.

MIPI consisted of age, performance status, LDH and WBC. It was divided into three risk groups - low risk (44% patients, median overall survival (OS) not reached); intermediate risk (35% of patients, median OS at 51 months); and high risk (21% patients, median OS at 29 months).[20] A study done in Europe showed that majority of patients with MCL had intermediate

or high risk. In contrast, this study showed all of the three MCL were equally distributed in the three risk groups.

Follicular Lymphoma Internal Prognostic Index (FLIPI) consisted of age, Ann-arbor stage, hemoglobin level, LDH, and number of nodal sites. It was divided into three risk groups - low risk (five and ten-year OS of 91% and 71%, respectively); intermediate risk (five and ten-year OS of 78% and 51%, respectively); and high risk (five and ten-year OS of 53% and 36%, respectively).[21,22] In this study, majority of the cases were low or intermediate risk.

The clinical aggressiveness of a FL was correlated with the number of centroblasts.[5] The number of centroblasts formed the basis of classifying FL into three major grades – grade one (less than six centroblasts/hpf), grade two (six -15 centroblasts/hpf), and grade three (>15 centroblasts/hpf). In this study, majority of the FL had grade one histology.

Both the FLIPI and grade may predict risk of histologic transformation. FL with high risk FLIPI and grade were at greater risk of histologic transformation.[5,8,22] In this study, one case documented in the process of histologic transformation had a high risk FLIPI and grade three histology.

Treatment Outcomes Profile

In this study, those who had chemotherapy were treated with CHOP or R-CHOP. A study showed that bendamustine plus rituximab had higher PFS and fewer adverse events than R-CHOP.[23] In the Philippines, due to financial constraints, most with NHL were treated with CHOP with or without rituximab, because it was relatively cheaper; it could also be covered by the national health insurance program of the Philippines – the Philhealth.

In this study, those who had surgery were mostly GI and thyroid MZL consistent with the standard of care. The present guidelines for extranodal MZL recommended surgery for resectable masses located in the thyroid, colon, small bowel, lung and breast.[7]

In this study, those who had no active intervention generally had disease control lasting up to two years. Indolent lymhoma (IL) had a slow growing biology and generally incurable with conventional chemotherapy.[2,5,8] Weighing the risk of possible adverse event or complications, observations could be the more prudent choice if asymptomatic.

In this study, those who had combined modality therapy were mostly FL. Post-chemotherapy radiation was given if with residual disease as in this case, consistent with the standard of care.[8,23]

Most of the patients in this study did not follow-up which may affect the results.

Lymphoma by Location

Thyroid Lymphoma

In this study, both cases of thyroid lymphoma were MZL. One was male in his fourth decade, pre-operative biochemically euthyroid; the other was female in her fifth decade, pre-operative hypothyroid on levothyroxine, with a history of Hashimoto's thyroiditis.

Thyroid lymphoma was a rare malignancy of the thyroid gland usually comprising one to five percent and one to seven percent of all thyroid cancers and lymphomas, respectively. It could be seen in elderly (>60 years old) females primarily presenting with an anterior neck mass. Histology was primarily MZL and DLBCL. Clinical features that would favor thyroid lymphoma would be a history of Hashimoto's thyroiditis, tumor size less than seven cm, obstructive symptoms and a rapid growth of a firm, diffuse thyroid mass. A retrospective study done in Filipino patients showed that thyroid lymphomas occurred at a lower mean age (<60 years old) with more presenting with a MZL histology. In this study, both cases did not present with symptoms of obstruction but one had a histologically confirmed Hashimoto's thyroiditis.[24] Both cases with thyroid lymphoma underwent surgery, consistent with the standard of care.

Gastro-intestinal (GI) Lymphoma

The most common location of extranodal NHL was the GI tract, usually in the stomach. Although the most common histology for GI lymphoma was DLBCL, MZL and FL were also observed.[25] In this study, majority of the cases were located in the colon, limited stage, with MZL or SLL histology. Primary colorectal lymphoma was a rare disease with most cases usually presenting as an extension of a more wide spread disease.

In this study, most cases presented with abdominal pain as the chief complaint, consistent with the reported literature. Other symptoms, reported in some studies included weight loss, and GI bleeding. Obstruction and perforation, both rare in GI lymphoma, were not observed for the cases included in this study.[5,25]

Management of GI lymphoma (indolent and aggressive) depended on the histology of the malignancy. Low-grade lymphomas could be managed several ways depending on the location, presence of symptoms, and presence of co-morbidities.[7] For non-gastric MALToma, radiotherapy was the preferred diagnostic modality provided that the patient had good performance status.

However, guidelines also recommended surgery as an alternative to radiotherapy for MZL located in the lung, breast,

thyroid, colon, and small bowel. In this study, most cases had surgery usually hemicolectomy, as treatment intervention. Other options were targeted therapy or observation.[26]

Conclusion

Small lymphocytic lymphoma (SLL) was the predominant type of IL at the PGH-CI. Most cases seen were elderly, usually aged 40 years old and above, except for FL mostly seen for those aged 50 years old and above. Low sample size was attributed to various factors such as the inherent rarity of IL; certain Filipino traits and values; relatively imperfect procedure in specimen handling; and relatively lack of expertise in hematopathology.

Indolent lymphoma (IL) was more common in males, especially for MZL and SLL. It also showed that most had B symptoms and limited disease, in contrast to aggressive lymphomas such as DLBCL. It demonstrated that majority presented with an orbital mass, mostly with MZL histology. FL had mostly low-risk FLIPI and low grade histology.

Indolent lymphoma (IL) which received chemotherapy had disease control with at least four cycles of CHOP. Those who had surgery had a MZL histology; about half had disease control for up to nine months only. Those who did not undergo any active intervention had disease control for up to two years. Due to the long duration of disease control, observation as intervention for asymptomatic patients with IL remained a viable option.

The clinico-pathologic profile presented in the study may be limited by the fact that certain work-ups such BMA and whole body CT scan recommended as standard of care were not always done.

Recommendations

The authors recommend biopsy of solid tissues even in patients confirmed to have CLL in order to document SLL. They recommend further study of factors influencing understaging as this will affect prognosis and treatment.

Glossary

1. Indolent Lymphoma – malignancies of predominantly small lymphocytes with monoclonal proliferation of mature B-cells expressing surface immunoglobulin in a light- and heavy-chain restricted manner with low proliferative rate explaining its long median survival and general incurability of disease with conventional chemotherapy. It consists of FL, MCL, MZL, SLL and WM/LPL (Grogan, 1996).
2. Limited-stage IL – includes stage I and II lymphoma.
3. Advanced-stage IL – includes stage III and IV lymphoma.
4. Disease outcomes – includes any of the following: complete response, stable disease, partial response, progressive disease or recurrence.
5. Complete response (CR) – complete disappearance of detectable disease; nodes >1.5 cm before therapy regress to <1.5cm; nodes 1.1 to 1.5 cm in long axis and >1.0 cm in short axis shrink to ≤1.0 cm in short axis.
6. Partial response (PR) - greater than 50% decrease in in the sum of the diameters in up to six nodal masses or in hepatic or splenic nodules.
7. Stable disease (SD) – neither PR nor relapse/progression
8. Relapse or Progression - new or increase in size of mass or lymph node
9. Disease control – CR, PR and SD

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