Primary breast lymphoma: A single center study

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Abstract. The aim of the present study was to summarize the clinical characteristics of primary breast lymphoma (PBL) and evaluate its management approaches. A total of 29 patients newly diagnosed with PBL, and treated between April 2006 and May 2013, were analyzed retrospectively. The median survival follow-up time for all patients was 66.8 (range, 25.4-110.0) months. The results of the follow-up revealed 22 living lymphoma-free patients and 7 patients who had succumbed to PBL. Of the 7 deceased patients, 6 had succumbed to lymphoma and 1 to chemotherapy-associated hepatic failure. In total, 1 patient who presented with bilateral breast lymphoma developed left breast relapse following lumpectomy and chemotherapy, 2 patients developed a bone marrow relapse, 1 patient developed lung and mediastinal lymph node relapses, and 1 patient developed a skin relapse. The Kaplan-Meier estimator predicted 5-year overall survival and progression-free survival rates for all patients of 74.4 and 74.6%, respectively. PBL appears to be a rare disease with a good overall prognosis and low incidence of local relapse, following chemotherapy alone or in combination with other treatments. Further studies investigating the development of effective agents for use in treatment-resistant patients are required.

Introduction

Primary breast lymphoma (PBL), a rare lymphoma subtype, was first described in 1959 (1), and accounts for <3% of extranodal lymphomas, ~1% of all non-Hodgkin lymphoma (NHL) and 0.5% of breast malignancies (2-7). Female patients account for >95% of PBL cases (3-13) and the most frequently occurring histological subtype is diffuse large B-cell lymphoma (DLBCL) (14). The definition of PBL, as proposed by Wiseman and Liao (15), and modified by Hugh *et al* (16), is the presence of breast tissue in close proximity to lymphoma, with no antecedent diagnosis of lymphoma and no extramammary disease other than ipsilateral axillary nodes (15,16). In addition, it has been suggested to include patients presenting with lymphoma of regional (supraclavicular and internal mammary) nodes and bilateral breast lymphoma (14).

Previously, the International Extranodal Lymphoma Study Group reported the largest retrospective series of 204 patients with PBL and concluded that the combination of limited surgery, anthracycline-containing chemotherapy, and involved-field radiotherapy produced the best outcome for PBL (5). For patients with primary breast DLBCL, rituximab was recommended (14). However, due to the limited number of patients, prolonged time span, combined primary and secondary breast involvement, and low- and high-grade malignant lymphomas, PBL prognosis remains poorly defined. The purpose of the present study was to summarize the clinical characteristics of PBL and evaluate its management approaches.

Materials and methods

Patients and patient workup. Ethical approval was obtained from the Independent Ethics Committee of Zhejiang Cancer Hospital (Hangzhou, China). A total of 29 patients (1 male and 28 female) newly diagnosed with PBL and treated between April 2006 and May 2013 were retrospectively evaluated. All records were considered valuable if there was available data on patient demographics, pathological diagnoses, tumor details, therapeutic outcomes and follow-ups.

The pretreatment workup included obtaining a complete patient history and conducting a physical examination, liver and renal biochemical analysis, complete blood cell count, bone marrow biopsy, and computed tomography of the chest, abdomen and pelvis. Staging classification was performed according to the Ann Arbor classification (17) and histopathological diagnosis was based on the World Health Organization nomenclature (18).

When data were available, the stage-modified international prognostic index (IPI) score was defined for each patient included in the study. This score was established by Miller *et al* (19) and gives one point each for age, increased serum lactate dehydrogenase (LDH) and Eastern Cooperative Oncology Group (ECOG) performance status 2 or higher.

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Treatment protocol. Following diagnosis of DLBCL using a core needle or surgery, chemotherapy alone or in combination with radiotherapy was administered. The chemotherapy consisted of between 4 and 6 cycles of treatment with cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) or a CHOP-like regimen. Chemotherapy was administered with or without central nervous system (CNS) prophylaxis, consisting of intrathecal methotrexate or cytarabine. The radiotherapy consisted of treatment with between 15 and 25 site-directed radiotherapy sessions, of between 1.8 and 2.0 Gy/session (total, 30-46 Gy), in the month following the completion of the chemotherapy program. Rituximab was recommended for patients with primary breast DLBCL. For other PBL histological subtypes, treatment was confirmed by the multidisciplinary lymphoma team of Zhejiang Cancer Hospital. The efficacy of treatment was assessed according to the International Workshop to standardize response criteria for NHLs (20).

Follow-up and statistical analysis. Follow-up was performed by the oncologic outpatient clinic, and patients or relatives were contacted by telephone. The final follow-up was in June 2015. SPSS (version 17.0; SPSS, Inc., Chicago, IL, USA) software was used for statistical analysis. Kaplan-Meier estimators were used to calculate the overall survival (OS) and progression-free survival (PFS) rates. OS was measured from the date of diagnosis to the date of death or final follow-up. PFS was defined as the length of time from the date of diagnosis to the date of initial disease progression or death. Survival curves were plotted using the Kaplan-Meier estimator and compared using the log-rank test. Univariate analysis was performed to determine prognostic factors. $P<0.05$ was considered to indicate a statistically significant difference and all P-values were two-tailed.

Results

Baseline characteristics. A total of 29 patients were analyzed retrospectively. The baseline characteristics are listed in Table I. In total, 28 patients were female (96.6%) and 1 patient was male (3.4%). The median age was 50 years (range, 24-69). None of the patients had a previous history of benign or malignant breast disease, or breast implantation. The most frequent presentation was with a palpable mass (96.6%) and 3.4% presented with palpable axillary lymph nodes. Left breast involvement was similar to right (44.8 vs. 41.4%, respectively) and 4 (13.8%) patients presented with bilateral breast involvement. The median tumor size was 4 cm (range, 1-10 cm). A total of 16 (55.2%) patients presented with stage IE disease and 13 (44.8%) with stage IIE. A total of 2 (6.9%) patients presented with B-symptoms. The majority of patients (72.4%) presented with a low stage-modified IPI score of between 0 and 1. The most frequent histopathological types were as follows: DLBCL, 82.8%; marginal zone lymphoma (MZL), 6.9%; anaplastic large cell lymphoma (ALCL), 6.9%; and mantle cell lymphoma (MCL), 3.4%. Germinal center (GC) or non-germinal center (non-GC) phenotypic information based on immunohistochemistry using the Hans method (21) were available in 14/24 patients with DLBCL: GC, 6 patients; non-GCB, 8 patients; and undefined, 10 patients.

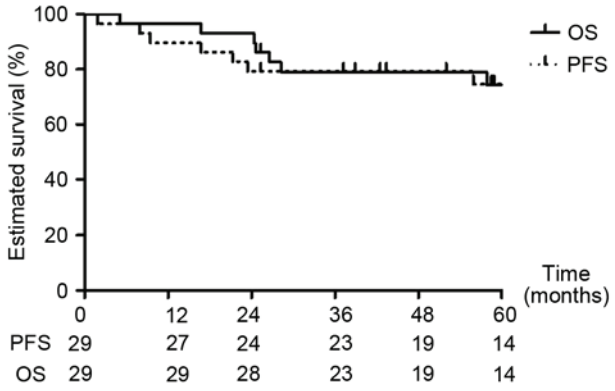

Figure 1. Kaplan-Meier curve showing the OS and PFS rates of patients with primary breast lymphoma in the present study. OS, overall survival; PFS, progression-free survival.

Treatment and response. The first-line therapy administered is summarized in Table II. The majority of patients (93.1%) received chemotherapy, of which four patients received CNS prophylaxis consisting of intrathecal methotrexate (n=3), or cytarabine (n=1). The chemotherapeutic treatment regime was supplemented with rituximab in 11 patients. Radiation therapy was administered in 13 (44.8%) patients to give a median total dose of 36 Gy (range, 30-46 Gy). Among the 27 patients treated with chemotherapy: 21 (77.8%) exhibited a complete response; 5 (18.5%) exhibited a partial response; and 1 (3.7%) exhibited disease progression.

The median follow-up time for all patients was 66.8 (range, 25.4-110.0) months. By the final follow-up session, 22 patients were alive without lymphoma and 7 patients had succumbed to PBL. A total of 6 patients succumbed to lymphoma-associated mortality, including 1 patient who developed progressive disease during chemotherapy, and 1 patient succumbed to chemotherapy-associated hepatic failure. Among the 5 patients who relapsed, 4 (80.0%) relapsed within the first two years. One patient who presented with bilateral breast involvement developed left breast relapse following lumpectomy and chemotherapy, 2 patients developed lymphoma of the bone marrow, 1 patient developed relapses of the lung and mediastinal lymph nodes, and 1 patient developed lymphoma of the skin. No patients developed relapses of the CNS. Kaplan-Meier estimator analysis predicted the 1-, 3- and 5-year PFS rates of all patients to be 89.7, 79.3 and 74.6%, respectively (Fig. 1). Kaplan-Meier estimator analysis predicted the 1-, 3- and 5-year OS rates to be 96.6, 79.0 and 74.4%, respectively (Fig. 1).

Outcome in patients with MZL, ALCL and MCL. The patient with MZL, who received a lumpectomy and five cycles of treatment with CHOP, was alive and disease-free by the final follow-up session. Of the 2 patients with ALCL, the patient who received a lumpectomy, five cycles of treatment with CHOP and 36 Gy of radiotherapy (18 sessions/day at 2.0 Gy/session), succumbed to lung and mediastinal lymph node relapse after 26.6 months. The other patient, who received hyperfractionated cyclophosphamide, vincristine, Adriamycin and dexamethasone/1A alternating with high-dose methotrexate and cytarabine/1B was alive and

Table I. Clinical characteristics of the 29 patients evaluated.

Characteristic	Patient no., %
Gender	
Male	1 (3.4)
Female	28 (96.6)
Age, years	
Median	50
Range	24-69
ECOG performance status at presentation	
0	14 (48.3)
1	15 (51.7)
Laterality	
Right	12 (41.4)
Left	13 (44.8)
Bilateral	4 (13.8)
Tumor size[a], cm	
Median	4
Range	1-10
Nodal site involvement at diagnosis	
None	16 (55.2)
Axillary	11 (37.9)
Supraclavicular + axillary	2 (6.9)
Pregnant at diagnosis	
Yes	0 (0.0)
Lactating at diagnosis	
Yes	1 (3.4)
No	28 (96.6)
Lactate dehydrogenase levels	
Elevated	8 (27.6)
Wild-type	21 (72.4)
Presence of B-symptoms	
Absent	27 (93.1)
Present	2 (6.9)
Ann Arbor stage	
IE	16 (55.2)
IIE	13 (44.8)
Adjusted IPI	
0	10 (34.5)
1	11 (37.9)
2	7 (24.1)
3	1 (3.4)
Pathological classification	
DLBCL	24 (82.8)
ALCL	2 (6.9)
MZL	2 (6.9)
MCL	1 (3.4)

[a]For bilateral cases, tumor size was measured as the larger value of the left and right breast diameters. ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma.

Table II. Summary of the first-line treatment administered.

Treatment type	Patient no., n (%)
Regime	
Surgery alone	2 (6.9)
Chemotherapy alone	3 (10.3)
Radiation and chemotherapy	5 (17.2)
Surgery and chemotherapy	11 (37.9)
Surgery, chemotherapy, and radiation	8 (27.6)
Surgery (n=21)	
Lumpectomy	16 (76.2)
Modified mastectomy[a]	5 (23.8)
Chemotherapy[b] (n=27)	
Anthracycline	27 (100.0)
Rituximab	11 (40.7)
Cycle no.	
<4	1 (3.7)
4-6	23 (85.2)
>6	3 (11.1)
Radiation	
Fields (n=13)	
Breast only	4 (30.8)
Breast and regional lymph nodes	9 (69.2)
Radiation dose (Gy)	
Median	36
Range	30-46

[a]Initially misdiagnosed as carcinoma of the breast; [b]4 patients receiving intrathecal chemotherapy.

disease-free by the final follow-up. Of the 2 patients with MCL, the patient who received a lumpectomy and six cycles of treatment with R-CHOP [rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2) and vincristine (1.4 mg/m^2, to a maximum of 2 mg), administered intravenously on day 1 and 100 mg oral prednisone on days 1-5] succumbed to a relapse of the bone marrow after 57.9 months. The other patient, who received a lumpectomy alone was alive and disease-free by the final follow-up.

Prognostic factors. The value of various potential prognostic factors, including age, ECOG performance status at presentation, tumor size, laterality, LDH levels, Ann Arbor stage, adjusted IPI value, surgery, cycles of chemotherapy received (>4), administration of rituximab and administration of radiotherapy, in predicting PFS and OS were evaluated. The impact of the prognostic factors is listed in Table III. The 5-year PFS rates for patients with bilateral and unilateral breast involvement were 50.0 and 78.4%, respectively (P=0.146 bilateral vs. unilateral). The 5-year OS for patients with bilateral and unilateral breast involvement was 50.0 and 78.1%, respectively (P=0.129 bilateral vs. unilateral). No statistically significant difference was observed in PFS and OS rates between the patients treated with rituximab and those without.

Table III. Univariate analysis of the impact of various prognostic factors on the results of treatment.

	5-year PFS		5-year OS	
Prognostic factor	Rate, %	P-value	Rate, %	P-value
Age		0.257		0.273
≥50 years	65.2		85.1	
<50 years	85.7		65.2	
ECOG performance status at presentation		0.666		0.617
0	77.1		77.1	
1	73.3		72.7	
Tumor size		0.812		0.886
≥4 cm	72.0		72.0	
<4 cm	78.6		78.6	
Laterality		0.146		0.129
Bilateral	50.0		50.0	
Unilateral	78.4		78.1	
Lactate dehydrogenase levels		0.281		0.309
Elevated	60.0		60.0	
Normal	81.0		80.4	
Ann Arbor stage		0.084		0.071
IE	85.9		85.6	
IIE	61.5		61.5	
Adjusted IPI		0.281		0.309
0-1	81.0		80.4	
2-3	60.0		60.0	
Surgery		0.848		0.809
Yes	74.7		74.2	
No	75.0		75.0	
Cycles of chemotherapy		0.398		0.437
>4	77.1		77.1	
≤4	66.7		62.5	
Rituximab administered		0.426		0.354
Yes	77.9		77.9	
No	68.8		68.2	
Radiotherapy received		0.379		0.397
Yes	83.3		83.3	
No	68.0		67.6	

PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index.

Discussion

Several collaborative investigations have been conducted to define the clinical characteristics of PBL and evaluate its management approaches (4,5,14). The criteria of PBL defined by Wiseman and Liao (15) were used in the majority of these studies. This definition has been challenged as it relies on an anatomic definition of the disease more appropriate when assessing solid tumors compared with lymphoma (11). In addition, the definition was based on a limited number of patients (11). However, there is insufficient data to revise the definition of PBL to include systemic NHL, as it is difficult to prove that the breast is the primary site of carcinogenesis (14). Therefore, the traditional criteria of PBL were used in the present study (14).

Clinically, the results of the present study were consistent with the published literature; the typical presentation was with a solitary, unilateral breast lump by a female aged between 50 and 60 years old (3-5,10-11). The most frequent histology is DLBCL and the median tumor diameter is 4 cm, although masses of <20 cm have been reported (5). In contrast to previous studies, the left breast was involved more frequently (44.8 vs. 41.4%) in the present study (3,5,9,12,13). In the present study, patients with PBL exhibited a 5-year OS rate of 74.4%. The 5-year OS rate has previously been reported to be between 48 and 75% (5,12,13), and is likely associated with the distribution of clinical characteristics and management approaches taken.

CNS relapse occurs in between 5 and 16% of patients with primary breast DLBCL (4,5,11,13). Increased rates of CNS relapse (3-year cumulative incidence, 23.6 vs. 1.4%; P<0.001) have been observed in a matched-pair analysis of primary breast and nodal DLBCL following treatment with R-CHOP (22). The 3-year OS rates were similar between the primary breast and nodal DLBCL groups (82.2 vs. 90.7%; P=0.345). The authors concluded that following treatment with rituximab, the clinical outcome of patients with primary breast DLBCL may no longer be inferior to those with nodal DLBCL. In a prospective study by Avilés *et al* (23), 0/32 patients with PBL developed CNS relapses following treatment with rituximab and dose-dense chemotherapy after a median follow-up of 64.5 months (range, 43-71 months). The majority of primary breast DLBCL CNS relapses occur <2 years subsequent to treatment completion (13). In the present study, 4 patients received CNS prophylaxis and 11 patients received treatment with rituximab. No patients developed CNS relapses after a median follow-up time of 66.8 (range, 25.4-110.0) months. This is likely due to the limited number of patients, retrospective nature of the study, and administration of intrathecal chemotherapy and rituximab.

None of the treatments used, including surgery, chemotherapy, radiotherapy and rituximab, were associated with OS and PFS rates (Table III). However, assessment of the association between treatment type and survival was limited due to the retrospective nature of the present study and the limited number of patients included. The only randomized comparison to date demonstrated a significantly improved survival rate in patients who received combined chemotherapy and radiotherapy, compared with chemotherapy or radiotherapy alone (24). In the present study, one patient, who presented with bilateral breast involvement, developed a relapse of the left breast following a lumpectomy and chemotherapy. Additionally, a meta-analysis demonstrated that radical surgery offers no benefit to patients with PBL (25). Although chemotherapy is now routinely supplemented with rituximab in patients with DLBCL (26), there are no prospective randomized clinical trials for the treatment of patients with PBL with rituximab.

PBL appears to be a rare disease and it is therefore difficult to characterize. However, the results of the present study suggest that the overall prognosis of patients with PBL is reasonable, and that the incidence of local relapse is low following chemotherapy alone or in combination with other treatments. Further studies into the development of effective agents for use in treatment-resistant patients are required.

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