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GENERAL GYNECOLOGY

Clinicopathologic features of the nine patients with primary diffuse large B cell lymphoma of the breast

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Abstract
Background Non-Hodgkin lymphomas of the breast are uncommon cancers that occur as either primary extranodal diseases or secondary localizations of a systemic disease. The term "primary breast lymphoma" (PBL) is used to define malignant lymphomas primarily occurring in the breast in the absence of previously detected lymphoma localizations. In this report, we analyzed nine patients with primary diffuse large B cell lymphoma (DLBCL) of breast.
Patients and methods Patients with newly diagnosed PBLs treated between 1997 and 2009 in five institutions were retrospectively evaluated.
Results The median age of the patients with PBL was 49 years (range 30–82 years), and four patients had left-sided and five had right-sided disease. All of the nine patients were classified as DLBCL. Five patients with DLBCL received chemotherapy followed by involved-field or elective-field radiotherapy and four received chemotherapy alone. Complete remission (CR) following primary treatment for all patients with PBL except for two cases was obtained. In two patients, recurrence occurred. At the median follow-up of 24.2 months, the 5-year OS rate was 76.2%. Univariate analysis indicated that age, ECOG PS, clinical stage, international prognostic index score, lactate dehydrogenase levels and the presence of B symptoms were not important prognostic factors in our study.
Conclusions Our series contained a small sample size, but it is interesting because it included only DLBCL cases. However, definitive conclusions about treatment and follow-up options of patients cannot be made in such a small series of patients. There are very few reports of patients with PBL treated with R-CHOP rather than CHOP alone. The followup is probably still too short and sample size very few to know how R-CHOP compares with CHOP-treated patients in other series, but this is definitely worth looking at in more detail when reasonable median follow-up has been achieved and sample size are sufficient.

Keywords Primary breast lymphoma · Diffuse large B cell lymphoma · Radiotherapy · Chemotherapy

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Introduction

Non-Hodgkin lymphomas (NHLs) of the breast are uncommon cancers that occur as either primary extranodal diseases or secondary localizations of a systemic disease. The term "primary breast lymphoma" (PBL) is used to define malignant lymphomas primarily occurring in the breast in the absence of previously detected lymphoma localizations. PBLs have a reported incidence of 0.04–0.5% of all breast malignancies. PBLs account for <1% of all patients with NHLs and approximately 1.7% of all extranodal NHLs [1, 2]. The criteria for the diagnosis of PBLs were defined by Wiseman and Liao [3] and include (a) adequate pathologic evaluation, (b) close association between lymphomatous infiltrate and mammary tissue and (c) the exclusion of either systemic lymphoma or extramammary lymphoma, except simultaneous ipsilateral axillary node involvement. Patients with breast involvement as a result of the progression or relapse of a previously diagnosed NHL are considered secondary breast lymphomas. With the exception of the recently published prospective Mexican trial [4] and the large study of the International Extranodal Lymphoma Study Group (IELSG) [5], in the literature there were only retrospective studies with a relatively limited number of patients, often together with cases of secondary breast involvement, single case reports and clinicopathological studies, the latter often lacking any follow-up information. So far, the largest retrospective series with genuine PBLs and sufficient follow-up identified 204 patients from the IELSG [5]. Other studies have included between 20 and 53 cases and provided some interesting information [1, 6–13]. However, the characteristics of this disease, such as natural history, prognostic factors and impact of treatment, have not yet been well established. In this report, we analyzed nine patients with primary diffuse large B cell lymphoma (DLBCL) of the breast.

Materials and methods

Patients with newly diagnosed PBLs treated between 1997 and 2009 in five institutions were retrospectively evaluated. The clinicopathological features, treatment modalities and outcomes were carefully reviewed from medical charts and pathology records. Those patients who received incomplete treatment or were lost to follow-up were excluded. The remaining patients were enrolled according to the criteria proposed by Wiseman and Liao [3] mentioned earlier. Clinicopathological features including age, gender, histopathological diagnosis, laterality, stage, lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, treatment modality, response to treatment, site of recurrence, disease status and survival status were assessed. Comprehensive history taking, physical examination, chest X-ray, computed tomography scans of the chest, abdomen and pelvis, bone marrow aspiration and biopsy were also performed for staging. More recently, positron emission tomography (PET) scans were performed in patients with aggressive histologies. The staging was based on the Ann Arbor staging system [14]. Histopathological diagnosis was based on the WHO nomenclature [15].

Statistical analysis

Statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA) software. Survival analysis and curves were established according to the Kaplan–Meier method and compared by the long-rank test. Disease-free survival (DFS) was defined as the time from the date of initial treatment to disease progression or recurrence or to the date of death or last known contact. Overall survival (OS) was described as the time from diagnosis to the date of the patient's death or last known contact [16]. Univariate and multivariate analyses of prognostic factors related to survival including age, stage, LDH level, ECOG performance status, international prognostic index (IPI) score, laterality of disease (left- or right-sided breast) and histopathology were performed by the Cox proportional hazards model. Multivariate p values were used to characterize the independence of these factors. A 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests and p values <0.05 were considered significant.

Results

A total of nine patients were analyzed retrospectively. The median follow-up time was 24.2 months (range 2.3–81.7). The clinicopathological features of these nine patients are listed in Table 1. All patients were women. The median age of the patients with PBLs was 49 years (range 30–82 years), and four patients had left-sided and five had right-sided disease. The majority of patients presented with a sign of tumor mass, a mass with local inflammation and palpable lymph nodes. Diagnosis was made with a core needle or an excisional biopsy of the all patients. All patients were classified as DLBCL. Two patients with PBL had normal LDH levels. Except for two patients with ECOG performance statuses (PS) 2, all of the patients had a good performance status (ECOG PS 0–1). Treatment was tailored to the clinical aggressiveness of the PBL (Table 2).

Table 1 Clinical characteristics of patients with primary non-Hodgkin's lymphoma of the breast

Patient no.	Age	Sex	Pathology	Localization	Stage	B symptom	LDH	ECOG PS	IPI
1	49	F	DLBCL	Right	1E	No	H	0	1
2	37	F	DLBCL	Left	2E	No	N	1	1
3	60	F	DLBCL	Right	2E	No	N	0	1
4	71	F	DLBCL	Right	1E	No	H	1	2
5	41	F	DLBCL	Left	2E	Yes	H	2	4
6	30	F	DLBCL	Left	2E	No	H	0	2
7	82	F	DLBCL	Left	2E	No	H	2	4
8	80	F	DLBCL	Right	2E	Yes	H	1	3
9	38	F	DLBCL	Right	2E	No	H	0	2

DLBCL diffuse large B cell lymphoma, *LDH* lactate dehydrogenase, *ECOC* Eastern Cooperative Oncology Group (ECOG) performance status

Table 2 Treatment and follow-up of patients with primary non-Hodgkin's lymphoma of the breast

Patient no.	Surgery	Chemotherapy	Radiotherapy	Responses	DFS/OS	Recurrence site	Salvage treatment
1	No	R-CHOP	Yes	CR	60+	–	–
2	No	R-CHOP	Yes	CR	24+	–	–
3	No	CHOP	Yes	CR	13/20	Cervical LAP	–
4	No	R-CVP	No	CR	28+	–	–
5	No	R-CHOP	Yes	CR	82/84	Abdomen	R-ICE
6	No	R-CHOP	No	PR	0/24+	–	Mini ICE-PBSCT
7	No	R-CHOP	No	–	0/2	–	–
8	No	R-CHOP	No	CR	18+	–	–
9	No	R-CHOP	Yes	CR	29+	–	–

DFS disease-free survival, *OS* overall survival; objective response was defined according to the WHO criteria. *CR* complete remission, *PR* partial response, *PD* progressive disease, *SD* stable disease, *R* Rituximab, *CHOP* cyclophosphamide, doxorubicin, vincristine, and prednisone, *CVP* cyclophosphamide, vincristine, prednisone, *ICE* Ifosphamide, carboplatine, etoposide, *PBSCT* peripheral blood stem cell

The pathological details of all patients cannot be obtained because our patients were collected from different cancer centers. In addition, EBV status of cases who were older than 60 years, cannot be detected due to same reason.

Five patients with DLBCL received chemotherapy followed by involved-field or elective-field radiotherapy, while four received chemotherapy alone (cases 4, 6–8). Anthracycline- or rituximab-containing regimens were administered as the initial systemic chemotherapy for seven patients with PBL. The area of elective-field radiotherapy included the uninvolved breast and supra-/infraclavicular lymphatics, as well as the axillary lymphatics. Complete remission (CR) following primary treatment for all patients with PBL except for cases 6 and 7 was obtained. Case 7 died during second cycle R-CHOP chemotherapy due to febrile neutropenia. Recurrence occurred in two patients (Table 2).

Case 3 was first treated with a CHOP regimen. Thereafter, recurrence occurred in the left cervical lymph nodes. The patient refused additional treatment modalities for this relapse and she died due to progressive disease.

Case 4 was interesting. This case has been reported previously [17]. The patient was first diagnosed with stage IIIB MALT lymphoma originating from the stomach. Thereafter, she was treated with surgery followed by a CVP regimen. Treatment was completed in six cycles and CR was obtained. She then presented with a mass in the upper outer quadrants of the right breast 8 years after the diagnosis of gastric lymphoma. Histopathological examination of the biopsy specimen revealed DLBCL of the breast with a post-germinal center phenotype. DLBCL was limited to breast was diagnosed. The patient received the combination therapy of rituximab, cyclophosphamide and vincristine on day 1 and prednisone on days 1–5 (R-CVP), every 3 weeks. CR was achieved after the completion of six cycles of chemotherapy. The patient had no specific symptoms and remained in remission during a follow-up of 28 months.

Case 5 received six cycles of the R-CHOP regimen and CR was achieved. After DFS for 7 years, she was admitted to our clinic with massive ascites and pleural effusion. Recurrence was confirmed by peritoneal biopsy. Planned

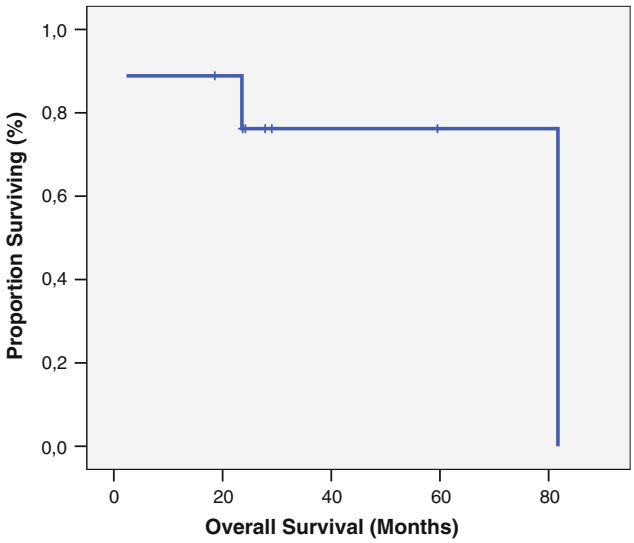

Fig. 1 Overall survival curves of patients with breast lymphoma

chemotherapy could not be administered because of the patient's poor ECOG PS and comorbidities and the patient died due to disease progression.

At the median follow-up of 24.2 months, the 5-year OS rate was 76.2% (Fig. 1). Univariate analysis indicated that age, ECOG PS, clinical stage, IPI score, LDH levels and the presence of B symptoms were not important prognostic factors in our study.

Discussion

In our study, the median age was 49 years, which is comparable to the 60–65 years range published by other authors [1, 4, 5, 7–9]. By contract, aggressive PBLs have sometimes been associated with younger ages [1]. PBL is extremely rare in males, with none of our 9 patients, 1 of the 23 patients from the M.D. Anderson Cancer Center, 1 of the 25 patients from the Mayo Clinic [9, 10] and none in the other series [1, 4, 7, 8]. In the present study, the most prominent initial signs were tumor mass, a mass with local inflammation and palpable lymph nodes. In the other series, a painless mass was the most commonly presenting sign in 80–100% of cases [7, 9]. According to the comprehensive literature review by Brogi and Harris, the majority of PBLs are DLBCL (40–70%) [5]. All of our cases were also DLBCL. Case 4 is first case with primary DLBC breast lymphoma diagnosed 8 years after gastric MALT lymphoma and she has recently been published as a case report in the literature.

Although the adverse effect of mastectomy can be influenced by other confounding factors, radical surgery is at best unnecessary option and should be avoided in PBL. Ideally, surgery should be limited to a biopsy to establish the correct histological diagnosis, leaving the treatment with curative intent to radiotherapy and chemotherapy [4, 5, 7]. In our series, mastectomy or lumpectomy were not performed in patients. The treatment approach of PBL patients is related to the lymphoma subtype. In the IELSG series, anthracycline-based chemotherapy was associated with higher OS [5]. Chemotherapy with R-CHOP is the current standard of care for patients with DLBCL. In our series, as in Table 2, seven of nine patients received R-CHOP, one patient was treated with R-CVP because of patient's low cardiac reserve and one patient received the CHOP regimen. After treatment, six patients achieved CR as disease-free, whereas three cases died due to the patient's refusal to receive treatment (case 3), disease progression (case 5) and febrile neutropenia (case 7), respectively.

Five of our patients (55.5%) received radiotherapy and all of them were treated with chemotherapy. In their series including 19 patients treated with definitive radiotherapy at MSKCC, De Blasio et al. [18] found a local control (LC) rate of 78%. The positive role of radiotherapy has also been suggested in the other series [5]. Our results together with the literature confirm the central role of radiotherapy in PBLs.

Aviles et al. [4] recently published their randomized trial of PBL in which 96 patients were allocated to radiotherapy ($n = 30$), chemotherapy ($n = 32$) and combined modality treatment ($n = 34$). All were staged IE or IIE PBL, with a good balance of prognostic factors among the three treatment groups. At 10 years, actuarial OS was 50, 50 and 76% ($p < 0.01$) in treatment groups, respectively [4]. A positive impact of combined modality in PBL has also been demonstrated in several retrospective series [5, 8–10]. In our study, five patients were treated with combined modality treatment. With regard to the outcome of patients with PBL, overall prognosis was only fair, with an overall 5-year survival rate of 53%. Even for stage IE, 5-year OS was only 62%. The 5-year survival rate reported in other series varied from 50 to 82% [4, 5, 9, 10, 13] and was likely to be related to the distribution of prognostic factors in the different series. In our series, 5-year OS rate was 76.2%, which was longer than the literature.

Unfortunately, in the most other series, information on LC rates is scarce. De Blasio et al. [18] report a 78% LC rate, whereas in Ganjoo's series no recurrence occurred in the involved breast [13]. In spite of these limited data, overall LC rates for patients receiving radiotherapy alone or combined with chemotherapy seems to be generally excellent. In our study, local recurrence was not detected.

In two patients relapsed was detected after a follow up of 13th and 82nd months, respectively (Table 2). A high rate of central nervous system (CNS) relapses in PBL was also found in other studies [4, 10, 12], and some authors

have raised the question of prophylactic CNS therapy [4, 5, 12]. However, CNS recurrence was not detected in our patients. As shown in studies by the Rare Cancer Network, the successful collection of data for rare cancers enabled us to define various prognostic factors. In univariate analyses, there was a borderline non-significant trend for a better 5-year survival rate in patients younger than 64 years. Stage IE was highly significantly better than stage IIE concerning OS, lymphoma-specific survival (LSS), DFS and LC. Concerning treatment, surgery had a significantly negative impact on OS and LSS, and radiotherapy a significantly positive effect on LSS and LC. Neither chemotherapy nor combined modality treatment significantly influenced OS, LSS or DFS, whereas combined modality had a significant impact on LC. In the multivariate analyses, early stage remained significant for OS, LSS, DFS and LC, tumor size for OS and LSS, whereas RT was significant only for LC. Prognostic factors were also found in other studies. In particular, Ann Arbor stage [7, 9, 10], IPI [5, 9] and grade [7] had a positive impact on OS and DFS. In our study, we found no prognostic factor by univariate analysis. This might be related to the small sample size of our study.

Conclusion

Our series contained a small sample size, but it is interesting because it included only DLBCL cases. However, definitive conclusions about treatment and follow-up options of patients cannot be made in such a small series of patients. There are very few reports of patients with PBL treated with R-CHOP rather than CHOP alone. The followup is probably still too short and sample size very few to know how R-CHOP compares with CHOP-treated patients in other series, but this is definitely worth looking at in more detail when reasonable median followup has been achieved and sample size are sufficient. Other series showed that a combination of chemotherapy and radiotherapy seems to be the best treatment option in these patients, but at least 26% of those with early stages and good prognostic factors die from tumor progression. It is, therefore, evident that other therapeutic options must be explored.

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Conflict of interest None.

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