Clinical characteristics of patients with B-cell lymphoma enrolled in clinical trials for aggressive lymphoma in Japan: Japan Clinical Oncology Group - Lymphoma Study Group study – JCOG0108A

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The clinical characteristics of B-cell lymphoma (BCL) were studied through the combined analysis of six clinical trials conducted by the Japan Clinical Oncology Group - Lymphoma Study Group (JCOG-LSG) for aggressive lymphoma in the 1990s, before the introduction of rituximab. Through a central pathological review, 829 patients were diagnosed with BCL according to the World Health Organization classification and treated with doxorubicin-containing combination chemotherapies. Of these patients, 642, 104, 30, and 24 patients were diagnosed with diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL), respectively. The overall survival (OS) of FL and MZL patients was higher than that of patients with DLBCL and MCL. The OS of the MCL patients was higher than that of DLBCL patients in the first 5 years, but MCL had the lowest survival after 5 years. The OS of DLBCL patients was clearly stratified by the international prognostic index and showed data compatible with that of aggressive lymphoma in the pre-rituximab era. These results established the clinical aspects of BCL in a large number of patients treated in prospective studies during the pre-rituximab era in Japan.

Keywords: aggressive lymphoma, B-cell lymphoma, diffuse large B-cell lymphoma, international prognostic index, clinical trials
according to geographic location. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of BCL both in Japan and in Western countries, while follicular lymphoma (FL) was found less frequently in Japan (6.7%) than in Western countries in the 1990s (11-33%).2,3 The second most common subtype of BCL in Japan in the 1990s was marginal zone lymphoma (MZL);2 however, the incidence of FL has gradually increased and has become the second most common subtype in Japan,4 which is similar to that observed in Western countries.3

Each lymphoma type has distinct pathological, immunophenotypic, molecular/cytogenetic, and clinical properties, responds differently to treatment, and has a distinct prognosis.5 There are many clinical and biological factors associated with these divergent treatment responses and prognoses, and prognostic models for various types of lymphoma have been proposed. For NHL, the international prognostic index (IPI) has been established as a useful prognostic model and applied to various types of NHL, including DLBCL.6 In Japan, the IPI has been shown to be a useful model for aggressive NHLs, such as DLBCL;7 however, prospective chemotherapy studies of a large number of Japanese patients with DLBCL conducted to determine the IPI’s validity have been limited.

The Japan Clinical Oncology Group - Lymphoma Study Group (JCOG-LSG) has conducted several clinical trials of combination chemotherapies for aggressive lymphoma. In these studies, patients were registered based on institutional pathological diagnoses according to the Working Formulation (WF) classification,8 and a central pathological review was conducted according to the World Health Organization (WHO) classification.9 To determine the clinical characteristics of malignant lymphoma in Japan based on the WHO classification, the JCOG-LSG conducted a combined analysis of these prospective studies, and the results of HL and peripheral T- and NK-cell lymphomas (PT/NKCLs) have been reported previously.10,11 In this study, we report the clinical characteristics of BCL after a combined analysis of the JCOG-LSG clinical trials.

MATERIALS AND METHODS

Details regarding the included studies’ designs, materials, and methods have been reported previously.10,11 The design of this study, JCOG0108A, is outlined below.

Patient selection

A total of 1,141 patients were enrolled in the following six JCOG-LSG multicenter clinical trials of adult, advanced, aggressive lymphomas according to the WF classification8 that were conducted consecutively in the 1990s: JCOG9002,12 JCOG9203,13 JCOG9505,14 JCOG9506,15 JCOG9508,16 and JCOG9809.17 The major eligible subtypes of BCL were as follows: diffuse large cells, diffuse small cleaved cells, diffuse mixed cells, large immunoblastic cells, follicular predominantly large cells, and small non-cleaved cell lymphomas.8 Patients with Mycosis Fungoides (MF), Sézary syndrome, adult T-cell leukemia-lymphoma, and precursor T-lymphoblastic leukemia/lymphoma were excluded from all the studies. Detailed descriptions of the eligibility criteria for these six trials have been previously reported.12-17 All the protocols described above, including the informed consent document, were approved by both the JCOG Protocol Review Committee and the institutional review board of each participating institution. JCOG0108A for NHL is an analysis of these six studies combined, and the first edition of JCOG0108A was written on June 27, 2001 and was approved by the JCOG Protocol Review Committee on October 31, 2001.

Treatment

All patients were enrolled in multicenter prospective studies and were treated with doxorubicin (DXR)-containing second- or third-generation multidrug combination chemotherapies in the JCOG9002 and JCOG9203 studies,12,13 or with cyclophosphamide (CPA), DXR, vincristine (VCR), and prednisolone (PSL) CHOP-like regimens in the JCOG9505, JCOG9506, JCOG9508, and JCOG9809 studies.14-17 JCOG9002 was a randomized phase III study evaluating the dose-intensification strategy for doxorubicin and cyclophosphamide in third-generation multi-agent combination chemotherapy, the LSG9 regimen with second-generation combination chemotherapy and the mLSG4 regimen, for patients with aggressive lymphoma.12 JCOG9203 was a phase II study of second-generation combination chemotherapy, the LSG12 regimen, for elderly patients with aggressive lymphoma.13 JCOG9505 was a randomized phase II study of CHOP every 2 weeks (CHOP-14) and dose-escalated CHOP for high-intermediate and high (H1/H)-risk patients with advanced-stage aggressive lymphoma.14 JCOG9506 was a phase II study of upfront, high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation for H1/H-risk patients with aggressive lymphoma.15 JCOG9508 was a phase II study of standard CHOP every 3 weeks (CHOP-21) for low and low-intermediate (L/LI)-risk patients with advanced-stage aggressive lymphoma.16 JCOG9809 was a randomized phase III study comparing CHOP-14 with standard CHOP-21 for patients with advanced-stage aggressive lymphoma in all IPI risk groups.17 All studies included newly-diagnosed patients, and JCOG9002, JCOG9203, and JCOG9809 were clinical trials including patients in all IPI risk groups.

Histopathological and immunohistochemical analyses by central review

An expert panel of six hematopathologists (Kiyoshi Mukai, Shigeo Nakamura, Koichi Ohshima, Masahiro Kikuchi, Yoshiohi Matsuno, and Tadashi Yoshino) and two clinicians (Tomomitsu Hotta and Masanori Shimoyama) reviewed the histopathologic diagnoses of 1,023 of the 1,141 patients who were enrolled in the six studies. A consensus diagnosis was reached following a histological review of each biopsy specimen in accordance with the third edition of the WHO classification system,9 by a panel of hematopathologists.
and clinicians as described previously. Briefly, immuno-
histochemical studies were conducted on paraffin sections
using the avidin-biotin-peroxidase complex technique and a
panel of monoclonal antibodies. Antibodies that were rou-
tinely used for the central review of the pathological diagno-
sis were for CD20 (L26; Dako, Glostrup, Denmark) and CD3
(PS1; Novocastra, Newcastle upon Tyne, UK). When fur-
ther immunohistochemical staining was necessary to estab-
lish a specific diagnosis, antibodies to the following antigens
were also used: cyclin D1 (SP4; Nichirei, Tokyo, Japan) for
MCL and CD10 (56C6; Novocastra) and bcl-2 (124; Dako)
for FL.

Response criteria
Response to treatment was evaluated according to the
WHO criteria. Complete response (CR) was defined as the
disappearance of all measurable lesions and symptoms of the
disease for at least 4 weeks. Partial response (PR) was
defined as a reduction of 50% or more in the products of the
perpendicular diameters of all measurable lesions added
together and the lack of the appearance of new lesions for at
least 4 weeks. Uncertain CR (CRu) was defined as mainte-
nance of PR without chemotherapy for more than 3 months
after completing treatment. Progressive disease (PD) was
defined as an increase of ≥ 25% in the size of any existing
lesion or the development of any new lesions. When there
were no signs of PD and the response also did not fulfill the
PR criteria, it was defined as no change (NC). The CR rate
was calculated by dividing the number of patients with CR or
CRUs by the total number of patients.

Statistical analysis
The OS was calculated from the date of enrollment in
each study until the last follow-up or date of death, and OS
curves were estimated using the Kaplan–Meier method. The
OS curves of B-NHL, PT/NKCL, and major histological
types of B-NHL (DLBCL, FL, MCL, and MZL) were ana-
lyzed. In patients with DLBCL, OS curves and CR rates
according to the IPI risk group were also presented. All sta-
tistical analyses were performed in the JCOG Data Center
using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC).

RESULTS
Table 1 summarizes the number of patients included in
the six clinical trials conducted by JCOG-LSG. A total of
1,141 patients were included in this study, and the number of
patients included in JCOG9002, JCOG9203, JCOG9505,
JCOG9506, JCOG9508, and JCOG9809 were 447, 45, 70,
43, 213, and 323, respectively. Of the 1,023 patients who
received central pathological reviews, 829 were diagnosed
with BCL and 136 were diagnosed with PT/NKCL. The
numbers of patients with major histological types of BCL
according to the WHO classification are summarized in Table
2. DLBCL was the most common type, followed by FL,
MCL, and MZL, which included extranodal MZL of mucosa-
associated lymphoid tissue (MALT lymphoma) and nodal
MZL.

The major clinical characteristics of each histological
type are summarized in Table 3. The patients with DLBCL
were predominantly male. Approximately two-thirds of the
patients had advanced disease, and most patients had a good
Eastern Cooperative Oncology Group (ECOG) performance
status (PS). Two-thirds of the patients with DLBCL were
categorized into the lower risk groups of the IPI.

Of the 104 patients with FL, 54% were male, 78% were
aged < 61 years, and three-quarters had advanced disease.
More than 80% of the patients did not have B-symptoms, and
85% were in the lower risk groups according to the IPI.

In MCL, two-thirds of the patients were male, one-third
of patients were older than 60 years, and around 90% were
in an advanced disease stage. Extranodal involvement was
observed in 40%, and more than 70% of patients were in the
lower IPI risk group.

Twenty-four patients were diagnosed with MZL. Half of
them were male, approximately two-thirds had advanced dis-
ease, over 90% had a good PS, one-third had more than one
extranodal site, and approximately 70% were in the lower
risk group according to the IPI.

Table 1. Number of patients registered in six JCOG-
LSG clinical trials

| JCOG study | No. of patients | (%) |
|------------|----------------|-----|
| JCOG9002(2) | 447            | 39.2 |
| JCOG9203(3) | 45             | 3.9 |
| JCOG9505(4) | 70             | 6.1 |
| JCOG9506(4) | 43             | 3.8 |
| JCOG9508(5) | 213            | 18.7 |
| JCOG9809(5) | 323            | 28.3 |
| Total       | 1141           |     |

Table 2. Number of patients diagnosed with each
B-cell lymphoma subtype

| B-Lbl | B-CLL/SLL | MCL | FL | Grade 1+2 | Grade 3 | MZL | DLBCL | PC | BCL-U | Total |
|-------|-----------|-----|----|----------|---------|-----|-------|----|-------|-------|
| 5     | 5         | 30  | 104| (59)     | (45)    | 24  | 642   | 1  | 18    | 829   |
| 1     | 0         |     |    | (7)      | (5)     |     |       |    |       |       |

B-Lbl, B-lymphoblastic lymphoma; B-CLL/SLL, B-chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; FL, follic-
ular lymphoma; MZL, marginal zone lymphoma; DLBCL, diffuse large B-cell lymphoma; PC, plas-
macytoma/myeloma; BCL-U, B-cell lymphoma, unclassified
The OS of the 759 patients with BCL consisting of MCL, FL grade 3, MZL, DLBCL, and unclassified BCL was better than that of patients with PT/NKCL (Fig. 1). The five-year OS was 60.4% (95% confidence interval [CI]: 56.7-63.8%) for B-cell lymphoma and 47.2% (95% CI: 38.6-55.4%) for PT/NKCL.

The OS of the BCL subtypes showed different patterns (Fig. 2). The five-year OS of patients with DLBCL, FL, MCL, and MZL were 58.6% (95% CI: 54.6-62.3%), 76.2% (95% CI: 66.6-83.4%), 59.2% (95% CI: 39.5-74.5%), and 82.9% (95% CI: 60.5-93.2%), respectively. DLBCL patients had the poorest OS in the first 5 years, whereas MCL showed the poorest survival after 5 years. The OS of the patients with FL, MCL, and MZL, however, decreased continuously over the observation period.

The OS of patients with DLBCL in relation to IPI is shown in Fig. 3. A total of two hundred and thirty-six patients with DLBCL (36.8%) were categorized as having low (L) risk, 193 (30.1%) as low-intermediate (LI) risk, 125 (19.5%) as high-intermediate risk (HI), and 67 (10.4%) as high (H) risk. The five-year OS of L, LI, HI, and H risk DLBCL were 75.7% (95% CI: 69.6-80.7%), 58.0% (95% CI: 50.6-64.7%), 43.5% (95% CI: 34.6-52.0%), and 22.4% (95% CI: 13.3-32.9%), respectively. The CR rates in the L, LI, HI, and H risk DLBCL groups were 80.3%, 72.1%, 57.9%, and 41.8%, respectively.

DISCUSSION

This study revealed the baseline clinical characteristics and treatment outcomes of a large number of patients who were enrolled in six clinical trials for aggressive lymphoma in the pre-rituximab era in Japan. Survival data for BCL in this study showed characteristic patterns. The OS of patients with BCL was higher than that of patients with PT/NKCL during the observation period. For the BCL subtypes, the OS of FL and MZL patients was better than that of DLBCL and MCL patients. The OS for DLBCL patients was

**Table 3. Clinical characteristics of the four major B-cell lymphoma subtypes, with percentages of each characteristic indicated**

| Characteristic | DLBCL (n=642) % | FL (n=104) % | MCL (n=30) % | MZL (n=24) % |
|---------------|----------------|--------------|-------------|-------------|
| Male          | Male 60 | 54 | 67 | 50 |
| Age > 60 years | 41 | 22 | 33 | 37 |
| CS 3 or 4     | 61 | 75 | 87 | 63 |
| PS > 1        | 16 | 7  | 7  | 4  |
| LDH > N       | 52 | 30 | 27 | 21 |
| No. of extranodal sites > 1 | 20 | 11 | 40 | 33 |
| B symptom, present | 24 | 18 | 30 | 21 |
| IPI (H/H)     | 30 | 12 | 27 | 21 |

CS, clinical stage; PS, performance status; IPI, international prognostic index; N, normal; H/H, high-intermediate risk and high risk

The OS of the patients with DLBCL consisting of MCL, FL grade 3, MZL, DLBCL, and unclassified BCL was better than that of patients with PT/NKCL (Fig. 1). The five-year OS was 60.4% (95% confidence interval [CI]: 56.7-63.8%) for B-cell lymphoma and 47.2% (95% CI: 38.6-55.4%) for PT/NKCL.

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poorest in the first 5 years and then decreased gradually after that, while for FL, MCL, and MZL, the OS decreased continuously throughout the observation period. For MCL patients, the OS curve decreased continuously and was inferior to that of DLBCL after 5 years. These results indicated that the OS of FL and MZL patients had the characteristic patterns of low-grade BCL patients, and the OS of MCL was similar to that of previous reports. Thus, the long-term prognosis of MCL was the worst among the four subtypes of BCL.

The survival of aggressive lymphoma could be stratified using IPI. The five-year OS rates of patients with aggressive lymphoma were 73%, 51%, 43%, and 26% in the L, LI, HI, and H risk groups, respectively. Since DLBCL is the most common type of aggressive lymphoma, survival data for aggressive lymphoma should be similar to that for DLBCL. In this study, the 5-year OS of DLBCL according to the IPI was 75.7%, 58.0%, 43.5%, and 22.4% for the L, LI, HI, and H risk groups, respectively. These data were comparable to those for aggressive lymphoma in the pre-rituximab era. In this study, a central pathological review conducted according to the WHO classification confirmed the diagnosis, and the data were collected from a large number of patients in prospective studies of aggressive lymphoma. Concerning the survival data for patients with DLBCL according to the IPI in the pre-rituximab era, there have been only two retrospective analysis reports. Thus, our data should serve as a reference for the survival of patients with DLBCL in prospective clinical trials in the pre-rituximab era.

A previous DLBCL gene expression profiling study identified germinal center B-cell (GCB)-like and activated B-cell (ABC)-like DLBCL subtypes diagnosed as GCB and non-GCB subtypes by immunohistochemical analysis. These subgroups exhibited distinct characteristics and prognoses, and therefore provided informative data. However, we could not perform immunohistochemical analysis of these subtypes in our study due to the limited number of collected tissue samples.

In general, patients with FL have widespread disease, and most are diagnosed with advanced-stage disease. Despite this, patients with FL are usually asymptomatic. The clinical characteristics of FL in this study coincided with those of FL in the literature. Most of the patients had a good PS, an absence of B-symptoms, a low IPI risk, and 75% were diagnosed with advanced stage disease. These results indicate that the clinical characteristics of patients with FL in this study were comparable to the general features of FL. According to the WHO, an FL grade 3 classification incorporates 3A and 3B subtypes with characteristic clinical features. Unfortunately, since we did not differentiate FL 3A and 3B in portions of our study we were unable to provide any data for these subtypes.

MCL is predominantly diagnosed in males, most present with advanced stage III or IV disease, and extranodal involvement is a common feature. In this study, approximately two-thirds of patients with MCL were male. 87% were in stages III or IV, and more than one extranodal disease site was observed in 40% of the patients. The prognosis of MCL patients was poorest among the four types of BCL in this study, and the survival curve showed a constant decrease, with no plateau phase observed. These results were therefore comparable to the general features of MCL. MZL includes two types of indolent lymphoma: MALT lymphoma and nodal MZL. In general, patients with MALT lymphoma usually present at stage I or II with extranodal disease, and nodal MZL involves peripheral lymph nodes. The advanced and localized stage of MZL showed relatively good survival patterns. Since the clinical trials in this combined analysis included patients with advanced-stage disease, the clinical characteristics of patients with MZL in this study were not typical of those with MZL. For example, 63% had advanced stage, 21% had B-symptoms, and 21% had HI/H risk according to the IPI. On the other hand, only 4% had a poor PS, and LDH was elevated in one-fifth of the patients, suggesting that these patients had relatively indolent clinical presentations. The OS of patients with MZL in this study was similar to that of patients with FL. These results indicate that the clinical picture and prognosis were similar to those of MZL in advanced stages.

In Japan, rituximab was approved for CD20-positive indolent B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma in June 2001, and approved for all types of CD20-positive B-cell lymphoma in June 2003. Consequently, we cannot exclude the possible influence of rituximab treatment on the survival data in our study because some patients might have been treated with rituximab after relapse, especially after June 2003 when rituximab was approved for all types of CD20-positive B-cell lymphoma. Since we did not collect treatment data after relapse in our study, we could not analyze the possible effect of rituximab treatment on survival.

This study has several limitations. Since all the clinical trials included in this combined analysis were conducted before the introduction of rituximab, data concerning prognosis could not be directly applied to the rituximab era. Second, this study included only patients eligible for clinical trials, and ineligible patients, such as those with poor PS, inadequate organ function, and elderly patients were excluded. Since the current study is a combined analysis of six studies for patients with various age groups and risk groups, and each study incorporated different treatment regimens, the treatment outcomes may be influenced by selection biases. In addition, only a few patients with FL, MZL, and MCL were included because the data were based on clinical trials for aggressive lymphoma. Thus, the proportions of lymphoma subtypes did not reflect a real-world situation, and therefore detailed survival analyses were difficult to conduct due to the small number of patients within the various subtypes.

In conclusion, this study shows that major types of BCL registered in clinical trials for aggressive lymphoma in the pre-rituximab era in Japan displayed characteristic clinical pictures and prognoses. DLBCL, the most common type of BCL, showed survival patterns according to IPI. Survival data were consistent with those of aggressive lymphoma in Japan, rituximab was approved for CD20-positive indolent B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma in June 2001, and approved for all types of CD20-positive B-cell lymphoma in June 2003. Consequently, we cannot exclude the possible influence of rituximab treatment on the survival data in our study because some patients might have been treated with rituximab after relapse, especially after June 2003 when rituximab was approved for all types of CD20-positive B-cell lymphoma. Since we did not collect treatment data after relapse in our study, we could not analyze the possible effect of rituximab treatment on survival.

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the pre-rituximab era.

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CONFLICTS OF INTEREST

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