Clinicopathologic characteristics and treatment outcome of the addition of rituximab to chemotherapy for CD5-positive in comparison with CD5-negative diffuse large B-cell lymphoma

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Received 3 July 2009; revised 2 November 2009; accepted 2 February 2010

Background: CD5-positive (CD5+) diffuse large B-cell lymphoma (DLBCL) comprises ~10% of DLBCLs, and it is associated with poor prognosis. The clinicopathologic characteristics and prognosis of CD5-negative (CD5−) DLBCL and CD5+ DLBCL were compared.

Patients and methods: The subjects were 607 DLBCL patients in whom cell surface markers could be analyzed, among 930 consecutive patients who were registered in the Adult Lymphoma Treatment Study Group between 1998 and 2008.

Results: In all, 102 patients (16.8%) had CD5+ DLBCL. Compared with CD5− DLBCL, CD5+ DLBCL was more closely associated with elevated serum lactate dehydrogenase level, advanced stage, poor performance status, extranodal sites, CD10− , BCL-2+, MUM1+, and nongerminatal center B-cell type. The 5-year overall survival (OS) rates of CD5+ DLBCL (n = 102) and CD5− DLBCL (n = 505) were 55% and 65%, respectively (P = 0.032), with 5-year progression-free survival (PFS) rates of 52% and 61%, respectively (P = 0.041). In the CD5+ DLBCL patients, the addition of rituximab to chemotherapy significantly improved PFS (4-year PFS, 47.4% versus 62.5%), but not OS (4-year OS, 57.8% versus 63.5%).

Conclusions: For CD5+ DLBCL, the addition of rituximab to chemotherapy significantly improved the PFS, but not OS. Therefore, it is thought that a new treatment strategy is necessary for CD5+ DLBCL.

Key words: CD5-positive diffuse large B-cell lymphoma, CyclOBEAP, nongerminatal center B-cell type, rituximab

Introduction

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 40%–50% of non-Hodgkin’s lymphomas and has heterogeneous clinical, histological, immunophenotypic, cytogenetic, and molecular features. De novo CD5-positive (CD5+) DLBCL is seen in ~10% of DLBCLs, and it is associated with poor prognosis. Patients with CD5+ DLBCL showed a higher age distribution, female predominance, aggressive clinical features, poor performance status (PS) of the Eastern Cooperative Oncology Group, and elevated serum lactate dehydrogenase (LDH) level compared with those with CD5-negative (CD5−) DLBCL [1]. Rituximab is highly effective against various types of B-cell lymphoma. The addition of rituximab to CHOP (combination chemotherapy with cyclophosphamide [CPA], doxorubicin [DXR], vincristine [VCR], and prednisone [PDN]) regimens has been found to improve the outcome of DLBCL [2]. Therefore, prognostic improvement of CD5+ DLBCL is expected by rituximab combination chemotherapy. Some studies have found that rituximab combination chemotherapy is associated with a favorable prognosis in CD5+ DLBCL. However, other studies found that there was no difference in prognosis between cases who received rituximab combination chemotherapy and those who did not receive rituximab combination chemotherapy. We therefore compared the clinicopathologic characteristics and prognosis upon rituximab combination chemotherapy of CD5− DLBCL and CD5+ DLBCL.

Patients and methods

Patients

The subjects were 607 DLBCL patients in whom cell surface markers could be analyzed by flow cytometry, among 930 consecutive patients who were registered in the Adult Lymphoma Treatment Study Group (ALTSG) in Japan between 1998 and 2008. In all, 102 patients (16.8%) had CD5+ DLBCL, and 45 of them received rituximab combination chemotherapy. Pathologic evaluation of the materials from each patient was carried out at
several central review meetings by six hematopathologists in the ALTSG pathology review board. A consensus diagnosis on each patient was obtained using the World Health Organization classification [3]. All specimens for histological and immunophenotypic studies were obtained at the time of initial presentation of the patients and were examined for CD5 antigen expression by flow cytometry. All patients were immunohistologically confirmed to be cyclin D1 negative.

All patients were newly diagnosed, were previously untreated, and received anthracycline-containing combination chemotherapy. Briefly, the CycloOBEAP (CPA, VCR, bleomycin, etoposide, DXR, and PDN) regimen [4] was primarily administered to younger patients (≤60 years old) with DLBCL, and the CHOP regimen was primarily administered to older patients (>60 years old). Rituximab was administered along with the CycloOBEAP or CHOP (R-CycloOBEAP or R-CHOP, respectively) regimen to the 297 patients who were diagnosed after 2005. The median follow-up period was 72 months (range 18–122 months). This study was approved by the Ethics Committee of Saitama Medical University, and complied with the Helsinki Declaration.

**morphological and immunophenotypic studies**

CD5+ DLBCL was diagnosed when the lymphoma cells were positive for CD5 by flow cytometric analysis. All of the CD5+ DLBCL specimens were reexamined by immunohistochemistry. Paraffin-embedded sections of each sample were immunostained with monoclonal antibodies against CD5 (Novocastra, Newcastle, UK), CD10 (Novocastra), CD20 (Novocastra), BCL-2 (DAKO, Glostrup, Denmark), BCL-6 (Novocastra), MUM-1 (DAKO), and Mib-1 (Novocastra). The 442 patients were assigned to the germinal center B-cell-like (GCB) group or the non-GCB group according to the classification method of Hans et al. [5]. In the immunostaining study using each antibody, the following categories were defined: negative (<30% positively stained tumor cells) and positive (≥30% positively stained tumor cells). The presence of Epstein–Barr virus (EBV) small RNAs (EBER) was positively stained tumor cells) and positive (hybridization using EBV-encoded small nuclear early-region oligonucleotides on formalin-fixed, paraffin-embedded sections.

**cytogenetic studies**

We used the standard technique for chromosome analysis [6]. Biopsied lymph nodes or other tumors were immediately disaggregated with scalpels in RPMI-1640 medium, and single cells were suspended in RPMI-1640 medium supplemented with 20% fetal bovine serum at a concentration of 10⁶ cells/ml. For the short-term unstimulated culture method, after the slides had been aged at 37°C/C for 4–7 days, the trypsin G-banding technique was used for analysis of karyotypes. Chromosome identification, karyotypic designation, and determination of clonality were carried out in accordance with the ISCN 1995: International System for Human Cytogenetic Nomenclature [7].

**statistical analysis**

All statistical analyses were carried out with SAS software (version 9; SAS Institute, Cary, NC). Differences in characteristics between the two groups were examined by the x² test, Fisher’s exact test, and Mann–Whitney U-test, and P <0.05 was taken to indicate significance. Progression-free survival (PFS) was calculated from the date of beginning chemotherapy to the date of progression or relapse or to the date of the last contact. Overall survival (OS) was calculated from the date of beginning chemotherapy to the date of death from any cause or to the date of the last contact. OS and PFS were used as parameters, and analysis was carried out according to the Kaplan–Meier method. The significance of differences in survival was assessed by the log-rank and generalized Wilcoxon tests. Differences between groups were evaluated by the Mann–Whitney U-test (nonparametric analysis). Multivariate analysis of prognosis was carried out using Cox’s proportional hazards regression model.

**results**

**clinical characteristics**

CD5+ DLBCL was seen in 102 (16.8%) of the 607 patients with DLBCL by flow cytometric analysis. The DLBCL patients were divided into the following two groups and their clinical characteristics were compared: patients with CD5+ DLBCL (n = 102) and those with CD5− DLBCL (n = 505) (Table 1). Advanced stage, high serum LDH level, poor PS, extranodal sites, and poor International Prognostic Index (IPI) were significantly more prevalent among patients with CD5+ DLBCL than among patients with CD5− DLBCL. Among the 102 patients with CD5+ DLBCL, extranodal sites of disease were bone marrow (42 patients), skin/subcutaneous tissue (9 patients), liver (1 patient), pleural effusion (6 patients), salivary gland (5 patients), adrenal gland (5 patients), stomach (4 patients), small intestine (4 patients), breast (4 patients), thyroid (4 patients), central nervous system (2 patients), and lung (2 patients). Thirty-seven patients had two or more extranodal localizations.

All 607 patients received chemotherapy. Among the patients with CD5+ DLBCL, we administered CycloOBEAP therapy to 18 patients, CHOP therapy to 39 patients, R-CycloOBEAP to 19 patients, and R-CHOP therapy to 26 patients. Among those with CD5− DLBCL, we administered CycloOBEAP therapy to 58 patients, CHOP therapy to 195 patients, R-CycloOBEAP to 114 patients, and R-CHOP therapy to 138 patients.

**immunophenotypic characteristics**

The immunohistochemical findings in the 607 patients (CD5+ DLBCL, 102 patients; CD5− DLBCL, 505 patients) are summarized in Table 2. Among the 102 patients who were positive for CD5 by flow cytometry, 63 patients (62%) were positive for CD5 by immunostaining. CD10 was positive in 9

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tr>
<td>Number of patients</td>
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</tr>
<tr>
<td>Number of patients</td>
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<tr>
<td>Age: median (range) (years)</td>
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<tr>
<td>Gender: male/female</td>
</tr>
<tr>
<td>Clinical stage: III/IV</td>
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<tr>
<td>B symptoms: no</td>
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<tr>
<td>Serum LDH: greater than normal</td>
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<tr>
<td>Performance status: 2–4</td>
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<tr>
<td>Bulky mass: present</td>
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<tr>
<td>International Prognostic Index: high-intermediate, high</td>
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<td>Extranodal disease: ≥2</td>
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CD5+, CD5 positive; DLBCL, diffuse large B-cell lymphoma; CD5−, CD5 negative; LDH, lactate dehydrogenase.
EBER was positive in 4.9% of the patients with CD5+ and in 6.1% of the patients with CD5+ DLBCL group. The proportion of patients with the GCB group and the non-GCB group, the GCB group consisted of 17 (16.7%) of the 102 patients with CD5+ DLBCL and in 80% of the patients with CD5+ DLBCL. The MUM-1-positive rate was significantly lower in the CD5+ DLBCL group than in the CD5− DLBCL group (P = 0.0004). BCL-2 was positive in 80% of the patients with CD5+ DLBCL and in 62.4% of the patients with CD5− DLBCL, showing a significant difference (P = 0.0006). BCL-6 was positive in 38.2% of the patients with CD5+ DLBCL and in 39.3% of the patients with CD5− DLBCL [not significant (NS)]. The MUM-1-positive rate was significantly higher in the CD5+ DLBCL group than in the CD5− DLBCL group (83.3% versus, 53.8%, P < 0.0001). EBER1 was positive in 4.9% of the patients with CD5+ DLBCL and in 61.1% of the patients with CD5− DLBCL (NS). When the 102 CD5+ DLBCL patients were divided into the GCB group and the non-GCB group, the GCB group consisted of 17 patients (16.7%) and the non-GCB group consisted of 85 patients. Among the patients with CD5− DLBCL, 42.9% were in the GCB group. The proportion of patients with the GCB type was significantly lower in the CD5+ DLBCL group than in the CD5− DLBCL group (P = 0.0001).

**Table 2.** Immunophenotypic features according to immunohistochemistry

<table>
<thead>
<tr>
<th>Subtype of DLBCL</th>
<th>CD5+ DLBCL</th>
<th>CD5− DLBCL</th>
<th>P value</th>
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<tr>
<td>GCB/non-GCB</td>
<td>17 (16.7%)/85</td>
<td>146 (42.9%)/194</td>
<td>&lt;0.0001</td>
</tr>
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CD5+, CD5 positive; DLBCL, diffuse large B-cell lymphoma; CD5−, CD5 negative; GCB, germinal center B-cell-like group.

(8.8%) of the 102 patients with CD5+ DLBCL and in 97 (19.6%) of the 494 patients with CD5− DLBCL. The CD10-positive rate was significantly lower in the CD5+ DLBCL group than in the CD5− DLBCL group (P = 0.0094). BCL-2 was positive in 80% of the patients with CD5+ DLBCL and in 62.4% of the patients with CD5− DLBCL, showing a significant difference (P = 0.0006). BCL-6 was positive in 38.2% of the patients with CD5+ DLBCL and in 39.3% of the patients with CD5− DLBCL [not significant (NS)]. The MUM-1-positive rate was significantly higher in the CD5+ DLBCL group than in the CD5− DLBCL group (83.3% versus, 53.8%, P < 0.0001). EBER1 was positive in 4.9% of the patients with CD5+ DLBCL and in 61.1% of the patients with CD5− DLBCL (NS). When the 102 CD5+ DLBCL patients were divided into the GCB group and the non-GCB group, the GCB group consisted of 17 patients (16.7%) and the non-GCB group consisted of 85 patients. Among the patients with CD5− DLBCL, 42.9% were in the GCB group. The proportion of patients with the GCB type was significantly lower in the CD5+ DLBCL group than in the CD5− DLBCL group (P = 0.0001).

**Chromosomal analysis of CD5+ DLBCL**

Chromosomal analysis was carried out in 66 of the 102 DLBCL patients, and 35 patients showed abnormal karyotypes. t(8;14)(q24;q32) was seen in two patients. These two patients were also positive for c-myc/IgH on FISH, but they were negative for CD10. Among the six patients with CD5+ DLBCL with 3q27 translocation, an Ig-type translocation [t(3;14)(q27;q32)] was seen in one patient. The other five patients with a non-Ig-type translocation had del(3)(q27). All six patients with 3q27 translocation showed positive immunostaining for BCL-6. t(14;18)(q32;q21.3) was seen in two patients. The most frequent translocation involved 19p13, which was observed in nine patients. One case each presented t(6;14)(q15;q32), t(2;14)(p13;q32), and t(1;14)(q12;q32). There were no patients with t(1;18)(q21;q21).

**Comparison of OS and PFS between the CD5+ DLBCL and the CD5− DLBCL groups**

Clinical follow-up data and information about first-line treatment were available in all patients. The complete response rate was 79.4% among patients with CD5+ DLBCL (n = 102) and 88.5% among patients with CD5− DLBCL (n = 505) (P = 0.02). The survival curves of the CD5+ DLBCL and the CD5− DLBCL groups are shown in Figure 1. The 5-year PFS was 52.2% among the patients with CD5+ DLBCL and 60.7% among the patients with CD5− DLBCL (P = 0.041) (Figure 1A). The CD5+ DLBCL group showed significantly poorer prognosis than the CD5− DLBCL group in terms of OS (P = 0.032) (Figure 1B).

**Comparison of OS and PFS between the CD5+ DLBCL patients who were treated with or without rituximab combination chemotherapy**

In the patients with CD5+ DLBCL, the 4-year PFS was 62.5% among the 45 patients who received rituximab combination chemotherapy and 47.4% among the 57 patients who did not receive rituximab combination chemotherapy, showing a statistically significant difference (P = 0.012) (Figure 2A). However, the 4-year OS was 63.5% among the patients who received rituximab combination chemotherapy and 57.8% among the patients who did not receive rituximab combination chemotherapy, showing no significant difference (Figure 2B). On the other hand, in the patients with CD5− DLBCL, the 4-year PFS was 70% among the 252 patients who received rituximab combination chemotherapy and 53% among the 252 patients who did not receive rituximab combination chemotherapy, showing a statistically significant difference (P < 0.0001) (data not shown). The 4-year OS was 76% among the CD5− DLBCL patients who received rituximab combination chemotherapy and 59% among those who did not receive rituximab combination chemotherapy, also showing a significant difference (P < 0.0001) (data not shown).

**Univariate and multivariate analyses of OS and PFS in patients with all DLBCLs**

Among all 607 patients with DLBCLs (CD5+ and CD5− DLBCLs), the OS was significantly worse for patients with the following characteristics: CD5+, age > 60 years, PS of two to four, LDH greater than normal, stage III/IV, more than one extranodal site, B symptoms, and not receiving rituximab combination chemotherapy (Table 3). Multivariate analysis of OS showed that age > 60 years, PS of two to four, B symptoms, and not receiving rituximab combination chemotherapy were independent negative prognostic factors (Table 3).

Among the 607 patients with DLBCLs, the PFS was significantly worse in patients with the following characteristics: CD5+, age > 60 years, LDH greater than normal, stage III/IV, poor PS, more than one extranodal site, B symptoms, and not receiving rituximab combination chemotherapy (data not shown). Multivariate analysis of PFS showed that age > 60 years, PS of two to four, B symptoms, and not receiving rituximab combination chemotherapy were independent negative prognostic factors (data not shown). CD5 status was not identified as a significant prognostic factor by multivariate analysis of OS and PFS.
univariate and multivariate analyses of OS and PFS in patients with CD5+ DLBCL

Among the 102 patients with CD5+ DLBCL, the OS was significantly worse in patients with the following characteristics: age >60 years, stage III/IV, poor PS, B symptoms, and extranodal sites more than two (data not shown). The PFS was significantly worse in patients with the following characteristics: age >60 years, stage III/IV, poor PS, B symptoms, extranodal sites more than two, and not receiving rituximab combination chemotherapy (data not shown). Multivariate analysis showed that age >60 years was the only independent prognostic factor of OS (hazard ratio: 5.2, 95% confidence interval 1.2–20.4). Multivariate analysis revealed that the five prognostic factors used to calculate the IPI score and non-GCB DLBCL were associated with OS and PFS. These results indicate that age >60 years and non-GCB type were independent prognostic factors that may predict both OS and PFS (data not shown).

**OS and PFS of patients with GCB and non-GCB CD5+ DLBCL**

When the patients were divided into the GCB DLBCL and non-GCB DLBCL groups, the 5-year OS rate was significantly lower in the non-GCB group (52.5%) than in the GCB group (93.3%) ($P = 0.0055$, Figure 3A). Upon the addition of rituximab to chemotherapy, the prognostic improvement of non-GCB DLBCL was not found (data not shown).

**comparison of OS and PFS according to the therapeutic method among the patients with CD5+ DLBCL**

Next, the PFS and OS were examined according to the therapeutic method. Among the patients with CD5+ DLBCL, CHOP therapy was carried out in 65 patients and CyclOBEAP...
therapy in 37 patients. The 5-year PFS among those who received CHOP therapy or CyclOBEAP therapy was 33.9% and 93.4%, respectively (P < 0.0001) (data not shown). The 5-year OS among those who received CHOP therapy or CyclOBEAP therapy was 38% and 93.4%, respectively (P < 0.0001) (Figure 3B).

**Discussion**

We described and compared the clinicopathologic characteristics and prognosis of 505 patients with CD5+ DLBCL and 102 patients with CD5+ DLBCL. CD5+ DLBCL comprised 16.8% of all DLBCLs in this study, and this study showed tendencies more than a previous report [1]. In this study, cell surface characteristics were studied in all cases. In order to make a diagnosis of CD5+ DLBCL, a study of cell surface characteristics is required. CD5+ DLBCL has been reported to be associated with elderly onset, female predominance, and frequent involvement of extranodal sites [1, 8]. In this study, compared with CD5− DLBCL, CD5+ DLBCL was more closely associated with elevated serum LDH level, advanced stage, poor PS, and extranodal sites. However, a sex difference was not observed. A significant difference in the presence of B symptoms was also not observed. Hyo et al. [9] reported a small number of patients with CD5+ DLBCL and compared them with patients with CD5− DLBCL and found that CD5+ DLBCL was associated with elevated serum LDH level, advanced stage, frequent involvement of extranodal sites, presence of B symptoms, and presence of bulky mass, but a sex difference was not found. Although that study included only a small number of cases of CD5+ DLBCL, there was no difference in prognosis between the CD5+ DLBCL cases and CD5− DLBCL cases.

Hans et al. [5] reported that non-GCB-type DLBCL had a significantly poorer prognosis than GCB-type DLBCL. In their study, the non-GCB type accounted for 58% of the DLBCL cases, and the 5-year OS of the GCB group was significantly higher than that of the non-GCB group. As to reports on patients with DLBCL who received rituximab combination chemotherapy, there is a report in which the cases were separated into the GCB DLBCL and non-GCB DLBCL groups and compared. Fu et al. [10] reported that the survival of patients with GCB DLBCL was still superior to that of patients with non-GCB DLBCL in the rituximab era. Lenz et al. [11] reported gene expression profiling in pretreatment biopsy specimens from 181 patients with DLBCL who received CHOP and 233 patients with this disease who received R-CHOP. Among the 233 patients who received R-CHOP therapy, GCB-type DLBCL accounted for 46%, activated B-cell-like (ABC)-type DLBCL accounted for 40%, and unclassified DLBCL accounted for 14%. GCB-type DLBCL was associated with a significantly better prognosis than ABC-type DLBCL among patients who received CHOP therapy and also among those who received R-CHOP therapy.

In our study, CD10 was positive in 8.8% and MUM-1 was positive in 83.3% of the CD5+ DLBCL cases. An analysis of genomic imbalance showed that the majority of CD5+ DLBCL cases were included in the GCB/ABC [12]. According to the Hans criteria [5], 83.3% of the CD5+ DLBCL patients examined in the present study had non-GCB DLBCL. In addition, the PFS and OS were significantly poorer in patients with the non-GCB type than in those with the GCB type. Our results indicate that CD5+ DLBCL of the non-GCB type has a poor prognosis. The present study also revealed that CD5+ DLBCL typically shows a CD10−, BCL-2+, and MUM1+ immunophenotype. BCL-2 is a member of the bcl-2 family of proteins that regulate programmed cell death [12]. Overexpression of BCL-2 protein in lymphoma cells has been incriminated in their resistance to chemotherapy both in vitro and in vivo. BCL-2 protein expression has been associated with poor prognosis among patients with DLBCL in the prerituximab era [13]. In contrast, several studies conducted in the rituximab era demonstrated that rituximab combination chemotherapy eliminated the prognostic significance of BCL-2 overexpression in DLBCL [14]. Ennishi et al. [15] reported that 10 of 11 patients with CD5+ DLBCL were positive for BCL-2, BCL-2 positive, CD5− DLBCL cases were compared with BCL-2 positive, CD5+ DLBCL cases, and the former group had a significantly better prognosis. In the present study, among the...
CD5+ DLBCL patients, the BCL-2-positive patients had significantly poorer prognosis in comparison with the BCL-2-negative patients \( (P = 0.002) \). However, among the CD5− DLBCL patients, there was no significant difference in prognosis between the BCL-2-positive patients and BCL-2-negative patients (data not shown). Therefore, it is suggested that the poor prognosis for patients with BCL-2 protein expression in the present series may have been influenced by CD5 expression.

Recently, R-CHOP therapy has become the standard chemotherapy for DLBCL. The Groupe d’Etude de Lymphome d’Adultes reported the first randomized controlled trial demonstrating the benefit of R-CHOP for the treatment of elderly patients with newly diagnosed DLBCL \[2, 16\]. Although the adoption of R-CHOP as the new standard of care has led to improved outcomes for this curable lymphoma, patients whose lymphoma is not cured by first-line therapy continue to pose a difficult challenge. Early identification of poor-risk patients may allow for alternative treatment strategies to be considered. Hyo et al. \[9\] administered R-CHOP chemotherapy for CD5+ DLBCL and reviewed the treatment outcome. The 2-year OS was 50%, and CHOP therapy did not result in a significant difference in prognosis from R-CHOP chemotherapy. We administered rituximab combination chemotherapy in 45 patients; the addition of rituximab to chemotherapy significantly improved the PFS, but not OS of the CD5+ DLBCL patients. A future large-scale study on the effectiveness of rituximab combination chemotherapy for CD5+ DLBCL is warranted.

Tagawa et al. \[17\], who analyzed CD5+ DLBCLs using array-based comparative genomic hybridization, demonstrated that CD5+ DLBCL had more frequent gain of 10p14–q15 and 19q13 and loss of 1q43–q44 and 8p23. Moreover, chromosomal changes were analyzed in 23 patients with CD5+ DLBCL by Yoshioka et al. \[18\]. In that study, chromosomal abnormalities of 8p21, 11q13, and 3q27 were commonly observed, and the OS was better in patients with 11q13 abnormalities than in patients with 8p21 abnormalities. Karnan et al. \[19\] reported that gain of 11q21–q24 or 16p was characteristic of CD5+ DLBCL and that some cases simultaneously showed gains of 11q21–q24 and 16p. They found that CD5+ DLBCL patients featuring 11q amplification had significantly better survival than CD5+ DLBCL patients with other translocations. In the present study, no patient presented 11q13 and 8p21, and the most frequent translocation involved 19p13. The number of cases will increase in the future, and it is hard to make clear whether chromosome abnormality is associated with a prognosis.

In summary, for CD5+ DLBCL, the addition of rituximab to chemotherapy significantly improved the PFS, but not OS. Therefore, it is thought that a new treatment strategy is necessary for CD5+ DLBCL.

disclosure

None of the authors declares a conflict of interest.