Diffuse large B-cell lymphoma (DLBCL) comprises a heterogeneous group with pathophysiological, genetic and clinical features. Many patients can be cured with R-CHOP therapy, which is the current standard regimen. Despite recent progress in improving patient survival, the 40% survival of DLBCL patients remains poor. Therefore, the most important issue for patients with DLBCL remains the development of a new front-line therapy. Several studies have reported that intensified chemotherapy with dose-adjusted EPOCH-R or R-ACVBP was superior to R-CHOP. Gene expression profiling has identified two distinct forms of DLBCL: activated B cell-like (ABC) and germinal center B-cell-like (GCB) types. ABC DLBCL exhibits a worse prognosis than GCB DLBCL by molecular diagnosis after R-CHOP therapy. Next-generation sequencing has identified unique oncogenic mechanisms and genetic complexity, which has provided rational therapeutic targets. There are also a number of biomarkers, including CD5, and prognostic factors. Efforts to distinguish many biomarkers will be crucial for individualized treatment in the future. [J Clin Exp Hematop 56(2):79-88, 2016]

Keywords: cell-of-origin, MYC, CD5, intravascular large B-cell lymphoma (IVLCL)
2-year EFS (57% vs. 38%) and 2-year OS (70% vs. 57%) improved the complete response (CR) rate (76% vs. 63%), \( p = 0.005 \). 8

For \( p < 0.0001 \) and 5-year OS (90.1% vs. 80.0%, \( p = 0.0263 \)), CHOP plus radiotherapy (RT) did not provide any advantage over CHOP alone for the treatment of low-risk, localized, aggressive lymphoma in elderly patients. 5 In the rituximab era, a phase II trial (S0014)6 with a matched historical control (S8736) was conducted in CD20-positive aggressive lymphoma patients with 0-1 risk factors of stage-modified IPI [non-bulky II stage, over 60 years old, PS 2-4, and higher serum LDH level] treated with 3 cycles of R-CHOP 21 (+ 1 cycle of R) followed by IFRT (40-46 Gy). The R-CHOP21 group had an improved 4-year PFS (76% vs. 63%) and 4-year OS (92%, 88%) compared with the CHOP group, with a median follow-up period of 5.3 years. However, either the PFS or OS curve shows a continuing pattern of relapse without a plateau. In limited stage disease, the addition of rituximab to CHOP has also been suggested to improve the outcome, but it may result in a smaller incremental benefit.

There are no large clinical trials using chemotherapy for patients with localized DLBCL only. In a randomized trial from 18 participating countries, a total of 824 young patients with DLBCL from 18 to 60 years of age with an age-adjusted international prognostic index (aa-IPI) score 0-1 were randomized to 6 cycles of R-CHOP(-like)14 therapy or 6 cycles of R-CHOP(-like)14 therapy (MInT). 7 Chemotherapy was followed by RT (30-40 Gy) for disease involving bulky mass over 5 cm. Overall, 72% of the patients had limited stage. The addition of R to CHOP was associated with a better outcome (3-year event-free survival [EFS] and OS). An updated analysis of the 72-months (mon) follow-up revealed that R-chemotherapy was significantly better than chemotherapy alone in the 6-year EFS (74.3% vs. 55.8%, \( p < 0.0001 \)) and 5-year OS (90.1% vs. 80.0%, \( p = 0.005 \)). 5 For all of these reasons, the standard therapy of non-bulky localized DLBCL has been considered either 3 cycles of R-CHOP followed by IFRT or 6-8 cycles of R-CHOP. These patients have a favorable prognosis; however, the necessity of IFRT, optimum total radiation dose, optimum number of cycles of R-CHOP, and biological differences are uncertain. In clinical practice, patients with localized DLBCL are administered treatment based on the individual patient profile (e.g., sites of disease, pathological lesion, age, organ function).

**Advanced DLBCL**

Standard of care for advanced DLBCL is R-CHOP chemotherapy (Table 1). It is based on the finding that the addition of rituximab to CHOP improved the outcome compared to CHOP. GELA conducted a phase III randomized trial in DLBCL patients with stage II-IV, 60-80 years of age, and PS 0-2, who were treated with 8 cycles of R-CHOP 21 (administered every 21 days) or 8 cycles of CHOP21. 9 R-CHOP21 improved the complete response (CR) rate (76% vs. 63%), 2-year EFS (57% vs. 38%) and 2-year OS (70% vs. 57%) compared to CHOP21. The updated analysis of the 10-year follow-up revealed that 10-year OS was significantly better with R-CHOP (43.5% vs. 27.6%). 10 In the pre-rituximab era, the German High Grade Non Hodgkin Lymphoma Study Group (DSHNHL) reported the results of a phase III trial and demonstrated that OS with six cycles of CHOP14, in which a dose-dense CHOP regimen was administered every 14 days under human recombinant granulocyte colony stimulating factor support, was superior to that with six cycles of CHOP21 in aggressive lymphoma patients 60 years and older. 11 Therefore, this group conducted their clinical study as a matter of the policy based on the decision that CHOP14 was a standard regimen in older patients with DLBCL. In the rituximab era, DSHNHL reported the results of a randomized 2x2 factorial trial of 6 vs. 8 cycles of CHOP14 with or without 8 cycles of R in CD20-positive B-cell lymphoma patients (80% of the patients; DLBCL) from 61 to 80 years of age with stage I-IV disease (RICOVER-60). 12 Patients treated with 6 cycles of R-CHOP14 followed by 2 cycles of R (-2R) had a significantly better EFS, PFS, and OS than did those treated with 6 cycles of CHOP14. There was no significant difference in outcome between 8 cycles of R-CHOP14 and 6 cycles of R-CHOP-2R. Toxicity in patients with 8 cycles of R-CHOP14 increased more markedly than in those who received 6 cycles of R-CHOP14. Thus, the optimal number of cycles of chemotherapy was considered to be six in older patients treated with R-CHOP14.

The results of two, large, randomized, phase III trials to verify the effect of R-CHOP14 against R-CHOP21 were revealed. In the United Kingdom - National Cancer Research Institute trial, 13 a total of 1,080 untreated DLBCL patients 18 years and older with stage I-IV disease were randomized to 6 cycles of R-CHOP14 or 8 cycles of R-CHOP21, with a median follow-up period of 46 mon. There were no significant differences in the CR rate, 2-year PFS, or OS (82.7% in R-CHOP14 vs. 80.8% in R-CHOP21; \( p = 0.3763 \)). In the LNH03-6B trial 14 by GELA, a total of 602 untreated DLBCL patients from 60 to 80 years of age with aa-IPI score of 1-3 were randomized to 8 cycles of R-CHOP14 or 8 cycles of R-CHOP21, with a median follow-up period of 56 mon. Similarly, there were no significant differences in the CR rate, 2-year EFS, PFS, or OS (69% in R-CHOP14 vs. 72% in R-CHOP21; \( p = 0.7486 \)). The rates of hematological toxicity (grade 3/4 neutropenia and febrile neutropenia) and infection were higher in the patients treated with R-CHOP21, whereas the rate of grade 3/4 thrombocytopenia and the frequency of red blood cell transfusion were higher in the patients treated with R-CHOP14. Therefore, R-CHOP21 was defined as a standard chemotherapy; however, it remains unclear whether 6 or 8 is the optimal number of cycles for R-CHOP21.

In the rituximab era, a dose-intensive treatment regimen
Treatment of DLBCL

has been attempted for younger high-risk DLBCL patients. The GELA conducted a randomized trial in a total of 380 patients with DLBCL from 18 to 59 years of age with an aa-IPI score of 0-1 comparing R-ACVBP with R-CHOP (LNH03-2B). Overall, 44% of the patients had limited-stage disease. The R-ACVBP group had an improved 3-year EFS (81% vs. 67%) and 3-year OS (92% vs. 84%) compared with the R-CHOP group, with a median follow-up period of 44 mon. However, due to the severe toxicity, this regimen seems not to be chosen in routine clinical practice. The value of high-dose chemotherapy followed by autologous stem-cell transplantation (ASCT) as a first-line therapy for younger patients with DLBCL has remained controversial in several randomized trials. SWOG conducted a phase III randomized trial (S9704) in DLBCL patients 15-65 years of age with an aa-IPI score of 2-3 by comparing 5 cycles of CHOP±R followed by 1 cycle of CHOP±R and ASCT with 3 cycles of CHOP±R. The ASCT group showed a significantly better 2-year PFS than did the CHOP±R group (69% vs. 55%, p = 0.005). In contrast, there was no significant difference in the 2-year OS (74%, 71%, p = 0.30). ASCT provided a therapeutic benefit (PFS, OS) only for those patients with a high risk based on the aa-IPI.

Elderly male patients had significantly lower R serum levels and worse outcomes in RICOVER-60. Subsequently, a phase II trial by DSHNHL reported that an increased dose of R (500 instead of 375 mg/m²) eliminated this risk in elderly male patients (SEXIE-R-CHOP-14). In the rituximab era, several studies of elderly DLBCL patients treated with CHOP combined with early dose-dense applications of R have been conducted by DSHNHL (DENSE-R-14, SMART-5-CHOP-14).

**CELL-OF-ORIGIN BASED APPROACH**

**GCB and ABC categorization**

Gene expression profiling has identified two distinct forms of DLBCL: ABC and GCB types, which were classified with the focus on the normal cellular counterpart of lymphoma, that is, GCB DLBCL appears to be derived from germinal center B cells and ABC DLBCL may be derived from a post-germinal center B-cell (cell-of-origin; COO). These forms were defined as molecular subgroups in the 2008 WHO classification. ABC DLBCL shows a more activated phenotype that is characterized by increased activity of the nuclear factor κB (NF-κB) pathway and a worse prognosis than GCB DLBCL. The 5-year PFS rate was 40% in ABC DLBCL and 74% in GCB DLBCL with R-CHOP.
Miyazaki K

explored principally because ABC DLBCL has a poor prognosis. To look for more effective therapeutic strategies, research attention has been promoted with a central focus on the molecular biology of ABC DLBCL regarding its pathogenesis, signal pathways, and gene mutations. In particular, both modifications of conventional R-CHOP chemotherapy itself and the addition R-CHOP to novel agents which have adequate rationale have been considered (Table 2).

Conventional chemotherapy

The National Cancer Institute conducted a phase II trial of a total of 72 untreated DLBCL patients 18 years and older with stage II-IV disease treated with dose-adjusted (DA)-EPOCH-R (rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy, which was an infusion regimen. The CR rate achieved was 94%. With a median follow-up period of 54 mon, the 5-year PFS and OS were 79% and 80%, respectively. Likewise, a phase II trial by the Cancer and Leukemia Group B (CALGB) of a total of 69 untreated DLBCL patients 18 years and older with stage II-IV disease treated with DA-EPOCH-R revealed that the CR rate, 5-year EFS, and 5-year OS were 84%, 75%, and 84%, respectively (CALGB 50103). This regimen showed a promising approach compared with the published data of R-CHOP and suggested a most relevant therapy for GCB DLBCL. Moreover, there was no significant difference in the PFS between GCB and non-GCB DLBCL from the results of the National Cancer Institute trial, and this regimen has received much attention as a treatment for non-GCB DLBCL. A randomized phase III trial comparing DA-EPOCH-R and R-CHOP (NCT01092182, Alliance 50303) is ongoing in the United States and its resulting conclusions, including a subgroup analysis of COO, are awaited. Among remaining trials, the LNH03-2B trial by GELA reported that the survival benefit related to R-ACVBP over R-CHOP is partly linked to improved survival among patients with non-GCB DLBCL.

Table 2. Cell-of-origin based therapy and outcome in diffuse large B-cell lymphoma

| Regimen [Reference] | DLBCL | Phase | Number | Stage | Response (ABC/non-GCB vs GCB) | Outcome (ABC/non-GCB vs GCB) |
|---------------------|-------|-------|--------|-------|------------------------------|-----------------------------|
| R-CHOP [23]         | Untreated | 233   | II-IV  |       |                              | 3-yr PFS: 40% vs 74%        |
| DA-EPOCH-R [24]     | Untreated | II    | 71     | II-IV |                              | 5-yr PFS: 56% vs 79%        |
| DA-EPOCH-R [25]     | Untreated | II    | 69     | II-IV |                              | 5-yr OS: 64% vs 84%         |
|                     |         |       |        |       |                              | 5-yr TTP: 67% vs 100%       |
|                     |         |       |        |       |                              | 5-yr EFS: 58% vs 94%        |
|                     |         |       |        |       |                              | 5-yr OS: 68% vs 94%         |
| Bortezomib + DA-EPOCH [27] | Relapse/Refractory | II | 27 | II-IV | ORR: 83% vs 13% CR: 42% vs 6% | median OS: 10.8 mon vs 3.4 mon |
| Lanalidomide [29]   | Relapse/Refractory | Retrospective | 40 | I-IV | ORR: 52.9% vs 8.7% CR: 29.4% vs 4.3% | median PFS: 6.2 mon vs 1.7 mon |
| Lanalidomide + R-CHOP [31] | Untreated | II | 32 | II-IV | ORR: 88% vs 88% CR: 88% vs 81% | median OS: 14 mon vs 13 mon |
| Lanalidomide + R-CHOP [30] | Untreated | II | 64 | II-IV |                              | 2-yr EFS: 74% vs 61%        |
|                     |         |       |        |       |                              | 2-yr PFS: 81% vs 71%        |
|                     |         |       |        |       |                              | 2-yr OS: 94% vs 88%         |
| Ibrutinib [25]      | Relapse/Refractory | I/II | 58 |       | ORR: 37% vs 5% CR: 16% vs 0% | median PFS: 2.02 mon vs 1.31 mon |
| Ibrutinib + R-CHOP [34] | Untreated | Ib | 11 | Bulky I-IV | ORR: 100% vs 100% CR: 100% vs 71% | median OS: 10.32 mon vs 3.35 mon |

DLBCL, diffuse large B-cell lymphoma; ABC, activated B-cell like; GCB, germinal center B-cell like; yr, year; mon, months; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; DA-EPOCH, dose-adjusted etoposide, vincristine, doxorubicin, cyclophosphamide and prednisone; PFS, progression-free survival; OS, overall survival; TTP, time to progression survival; EFS, event-free survival; ORR, overall response rate; CR, complete response rate
significantly higher than that of 15 patients with GCB DLBCL (83% vs. 13%, \( p = 0.004 \)). The median OS of patients with ABC DLBCL also showed a significantly better prognosis compared with the OS of those with GCB DLBCL (10.8 mon vs. 3.4 mon, \( p = 0.026 \)). There was no significant difference in outcome between 14 patients with GCB DLBCL and 18 patients with non-GCB DLBCL when treated with R-CHOP plus bortezomib (BR-CHOP).

A phase III randomized trial has been examined in untreated DLBCL comparing BR-CHOP with R-CHOP. This trial is unique in the identification of ABC/GCB DLBCL by real-time gene expression profiling analysis (NCT01324596).

**Immunomodulatory drugs**

Lenalidomide, an immunomodulatory drug, has a complex mechanism of action associated with immune modulation and anti-angiogenesis. This drug inhibits NF-κB activity in vitro and also exerts significant anti-tumor activity. A retrospective study of patients with relapsed/refractory DLBCL who received single-agent lenalidomide revealed that the ORR of 17 patients with non-GCB DLBCL was significantly better than that of 23 patients with GCB DLBCL (52.9% vs. 8.7%, \( p = 0.006 \)). Lenalidomide combined with R-CHOP (R2-CHOP) can be safely administered and is suggested to contribute to the improvement of non-GCB DLBCL, particularly in outcome. The British Columbia Cancer Agency (BCCA) and colleagues reported that the non-GCB and GCB subtypes had a similar outcome in stage II-IV DLBCL treated with 6 cycles of R2-CHOP. The Fondazione Italiana Linfomi group also reported that there was no difference in 2-year PFS (81% vs. 71%; \( p = 0.705 \)) and OS (94% vs. 88%; \( p = 0.58 \)) in patients with stage II-IV disease, 60-80 years of age, treated with 6 cycles of R2-CHOP between the non-GCB type and GCB type, with a median follow-up in survivors of 28 mon (REAL07). Several clinical trials, such as phase III trials comparing R-CHOP and R2CHOP and trials consisting of lenalidomide maintenance therapy, have been conducted on untreated DLBCL.

**BTK inhibitors**

Mutations of CD79B and CD79A, which are subunit components of the B-cell receptor (BCR), cause chronic activation of BCR signaling and result in the activation of the NF-κB pathway. Therefore, new therapeutic agents for the key enzyme and critical protein of BCR signaling have been developed to treat ABC DLBCL. Ibrutinib, Bruton’s tyrosine kinase (BTK) inhibitor, has been shown to be effective in treating several types of B-cell lymphomas driven by the activation of BCR, such as chronic lymphocytic leukemia, mantle cell lymphoma and ABC DLBCL. A phase I study of ibrutinib with R-CHOP reported good tolerance and an ORR of 100% in 18 patients with DLBCL. All non-GCB DLBCL patients (n = 4) achieved a CR; therefore, ibrutinib is expected to be a promising selective agent for non-GCB DLBCL. The results of a phase I/II study in patients with relapsed/refractory DLBCL treated with ibrutinib alone revealed the relationship between mutations and ORR in detail. In total, 71% of patients with mutant CD79B, 34% of patients with wild-type CD79B, and 80% of patients with both mutant CD79B/mutant MYD88 responded, whereas patients with wild-type CD79B and mutant MYD88, wild-type CARD11, and wild-type TNFAIP3 did not respond. The international, randomized, phase III trial of R-CHOP with or without ibrutinib for untreated non-GCB DLBCL classified by Hans’s method is registered (NCT018557502).

**MYC rearrangement/double hit lymphoma (Table 3)**

DLBCL with a MYC rearrangement (MYC+ DLBCL) comprises 4 to 14% of DLBCL cases and more patients are diagnosed with MYC+ DLBCL than with Burkitt’s lymphoma. Barrans S et al. reported that the OS was significantly worse for patients with a MYC rearrangement treated with R-CHOP. MYC+ DLBCL had a relatively high incidence of central nervous system (CNS) relapse compared with MYC- DLBCL. Savage KJ et al. also revealed that MYC+ DLBCL treated with R-CHOP had a significantly worse outcome than DLBCL without a MYC rearrangement. The 5-year OS rate was 33% in MYC+ DLBCL patients and 72% in patients with DLBCL without a MYC rearrangement (MYC- DLBCL). MYC+ DLBCL with an additional rearrangement of BCL2 (or, alternatively, BCL6) had a worse prognosis. B-cell lymphoma with multiple chromosome breakpoints (MYC, BCL2, BCL6) is described as “double-hit lymphoma (DHL)”. The 2008 WHO classification divides these diseases into B-cell lymphoma, unclassifiable, and with features intermediate between DLBCL and Burkitt’s lymphoma (intermediate DLBCL/BL); however, a retrospective analysis of 52 patients with DHL classified these as 29 cases of intermediate DLBCL/BL, 19 cases of DLBCL, and 4 cases of others. Due to a morphologic spectrum in which many cases have some resemblance to Burkitt’s lymphoma and some are more like DLBCL, DHL was not able to be diagnosed by histology alone. Moreover, the morphologic features in DHL do not have prognostic implications. Despite the clinical features of aggressiveness, DHL is classified as GCB type by immunohistochemistry. Fluorescence in situ hybridization (FISH) or chromosomal studies are needed for accurate diagnosis of DHL. To make a diagnosis of DHL, dual protein expression of MYC and BCL2 should be
performed by immunohistochemistry. DLBCL with MYC/BCL2 double-expression was associated with a poor prognosis.41-43 However, double-expressor DLBCL accounts for 29% of DLBCL42 and requires careful attention to distinguish this from “true” DHL.

The prognosis of DHL is markedly poor with R-CHOP. Moreover, it remains unclear which intensive therapy, such as a Burkitt’s-type regimen and HDC/ASCT, may offer a benefit.44 First-line treatment with R-EPOCH significantly reduced the risk of progression compared with R-CHOP in a meta-analysis.45 Several phase II clinical trials recruiting patients with DHL treated with R-EPOCH therapy are ongoing. Therapeutic novel agents for DHL, such as a bcl-2 inhibitor (ABT-199)46 and a suppressor of MYC expression (JQ1),47 are currently in clinical trials. In the next WHO classification, DHL may be categorized as another entity. In clinical practice, adequate identification of DHL with cytogenetic studies is of great clinical importance.

### Intravascular large B-cell lymphoma

Intravascular large B-cell lymphoma (IVLBCL) is one of subtype of DLBCL in the 2008 WHO classification and is pathologically characterized by selective growth of large tumor cells in the lumina of small vessels of systemic organs. IVLBCL is a rare disease, and hence, there have been no reports about results of prospective clinical trials. A retrospective study suggested a survival benefit with the addition of R to chemotherapy for IVLBCL; the 2-year OS for 49 patients treated with R-chemotherapy was significantly higher than that of 57 patients treated with chemotherapy alone (66% vs. 46%; \( p = 0.02 \)).48 In IVLBCL patients without CNS involvement at initial diagnosis, the risk of CNS recurrence at 3 years was 25% with a median follow-up in Table 3. Therapy and outcome in DLBCL with MYC rearrangement and double hit lymphoma

| Authors [Reference] | MYC+ DLBCL/DHL | Number | Regimen* | Outcome | Comment |
|---------------------|----------------|--------|----------|---------|---------|
| Barrans et al. [37] | MYC+ DLBCL     | 35     | R-CHOP   | 2-yr OS: 35% | MYC- DLBCL 2-yr OS: 61% |
| Johnson et al. [36] | DHL            | 54     | R-CHOP (11) CHOP (23) HD-chemo (6) | R-CHOP vs CHOP vs HD-chemo (median OS: 1.40 yr vs 0.42 yr vs 0.26 yr) |
| Savage et al. [38]  | MYC+ DLBCL     | 12     | R-CHOP | 5-yr PFS: 33% 5-yr OS: 33% | MYC- DLBCL (5-yr PFS: 60%, 5-yr OS: 72%) |
| Snuderl et al. [39] | DHL            | 20     | R-CHOP+ M (8), R-CHOP (3), R-ICE+ M/ato SCT (2), CHOP (1) Partially (1), Not known (1) | median OS: 4.5 mon | CNS involvement 45% |
| Li et al. [40]      | DHL            | 52     | R-Hyper CVAD (25) CODOX (1), other (1) | median OS: 18.6 mon 1-yr OS: 58% | R-CHOP vs intensive chemo median PFS (7.8 mon vs 21.6 mon) |
| Petrich et al. [44] | DHL            | 311    | R-CHOP (100), R-Hyper CVAD (65) DA-EPOCH-R (64), R-CODOX-MIVAC (42) other (24), R-ICE (9) (83 with consolidative SCT) | median PFS: 10.9 mon median OS: 21.9 mon 2-yr PFS: 40% 2-yr OS: 49% | OS was similar with and without consolidative SCT |
| Oki et al. [63]     | DHL            | 129    | R-CHOP (57), R-EPOCH (28) R-Hyper CVAD/MA (34), other (10) | R-CHOP vs R-EPOCH vs R-hyper CVAD vs other (2-yr OS: 41% vs 70% vs 44% vs 44%) |

MYC+ DLBCL, diffuse large B-cell lymphoma with MYC rearrangement; MYC- DLBCL, DLBCL without MYC rearrangement; yr, year; OS, overall survival; DHL, double hit lymphoma; R, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HD-chemo, high-dose chemotherapy; PFS, progression-free survival; CNS, central nerve system; EPOCH, etoposide, vincristine, doxorubicin, cyclophosphamide, predonison; M, methotrexate; CODOX-M/IvAC, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide and cytarabine; ICE, ifosfamide, carboplatin and etoposide; auto SCT, autologous stem cell transplantation; mon, months; DA, dose-adjusted; Hyper CVAD/MA, hyper fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with methotrexate and cytarabine

*The number in the parentheses indicates the number of patients treated with each regimen.
Treatment of DLBCL

CD5

CD5-positive (CD5+) DLBCL accounts for 10% of DLBCL cases and is associated with many clinical characteristics, such as elderly onset, advanced stage at diagnosis, elevated LDH level, and frequent involvement of extranodal sites.\(^{50,51}\) This immunohistochemical subgroup of DLBCL is not otherwise specified in the 2008 WHO classification. By gene expression profiling, most patients with CD5+ DLBCL are classified as ABC DLBCL.\(^{52}\) Immunohistochemically, 82% of CD5+ DLBCL cases are classified as the non-GCB type, and the BCL2 protein is positive in more than 70% of the patients. Despite the use of rituximab, the OS of patients with CD5+ DLBCL remains poor. The reason for this is that this disease is also characterized by a high incidence (13%) of CNS relapse compared with an incidence of approximately 5% for the all patients with DLBCL, even in the rituximab era.\(^{33}\) Moreover, 83% of the patients who experienced CNS relapse had brain parenchymal disease. More than 60% of patients with CD5+ DLBCL are older than 65 years at diagnosis and would therefore not be eligible for high-dose chemotherapy. DA-EPOCH-R was beneficial for Bcl-2 positive tumors, and its neurologic and cardiac toxicities are mild; therefore, it may be better suited for the elderly. Thus, we designed a new therapeutic strategy of DA-EPOCH-R combined with HD-MTX therapy, which is commonly used in the treatment of primary DLBCL of the CNS. This approach is potentially more effective than intrathecal administration of MTX to prevent CNS relapse of CD5+ DLBCL, particularly for brain parenchymal disease. The results of a phase II study of DA-EPOCH-R/HD-MTX for newly diagnosed CD5+ DLBCL (PEARL5 trial) are awaited (UMIN000008507).

Extranodal involvement

The incidence of CNS relapse in DLBCL has been reported to be 5% or less.\(^{54-56}\) Several clinical parameters, such as an elevated serum LDH level and extranodal or bone marrow involvement, have been established as risk factors for CNS relapse in DLBCL.\(^{57-59}\) Testicular involvement of DLBCL is associated with a particularly high risk of CNS relapse. A phase II study by the International Extranodal Lymphoma Study Group (IELSG) reported that R-CHOP with intrathecal administration of MTX followed by contralateral testicular irradiation could reduce the incidence of CNS relapse in testicular DLBCL.\(^{40}\) It remains undetermined whether patients who have involvement of extranodal sites other than the testis require CNS prophylaxis. Of the 3,840 untreated DLBCL patients who were treated with R-CHOP in the nine consecutive prospective trials of the DSHINHL, 292 patients had skeletal involvement that was associated with a poor prognosis.\(^{61}\) Additional RT to the skeletal sites improved the prognosis of the patients with skeletal involvement. Chemotherapy with RT may be considered standard care for patients with skeletal involvement. Prospective clinical trials based on therapeutic targets for each extranodal DLBCL are needed.

CONCLUSIONS

R-CHOP-based treatment has dramatically improved the prognosis of DLBCL over the past 20 years. High-risk patients who do not achieve adequate clinical results are needed to provide clues to the underlying causes of the disease. Chemotherapy combined with new therapeutic candidates is expected to lead to a breakthrough. In the future, therapeutic strategies of DLBCL, in terms of an individual biomarker algorithm, including immunohistochemistry, gene expression profiling, and cytogenetic analysis, are inevitable.

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DISCLOSURE STATEMENT

The author declares that there are no conflicts of interest regarding the present paper.

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Miyazaki K

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