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DIFFUSE LARGE B-CELL LYMPHOMA

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Summary of Literature Review

Introduction/Background

Diffuse large B-cell lymphoma (DLBCL) is an aggressive form of non-Hodgkin lymphoma (NHL) with subtypes that can be distinguished on the basis of immunophenotypic, morphologic, and molecular characteristics as well as clinical presentation [1]. Disease staging and choice of treatment, including the type, number, and sequence of chemotherapy agents and the need for consolidative radiation therapy (RT), should be made on the basis of clinical factors, which collectively determine response to therapy and survival. The anti-CD20 monoclonal antibody, rituximab, became part of the standard of care in the United States after its approval by the U.S. Food and Drug Administration in 1997; thus the existing literature on the diagnosis and treatment of DLBCL essentially can be separated into the pre-rituximab and post-rituximab eras. The current standard of care for disease at any stage is rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy (R-CHOP), although the number of chemotherapy cycles and use of consolidative RT are still being debated and are often determined based on location and extent of disease involvement.

The value of positron emission tomography/computed tomography (PET/CT) scanning in disease staging and response assessment is well established, however its role in treatment selection or interim treatment modification has yet to be established [2-4].

Diagnosis and Staging of DLBCL

DLBCL typically presents in people age 50 or older, although it can also present at any age and is slightly more common among men than women. Etiologic risk factors include HIV infection and low CD4 counts, although the prevalence of DLBCL among HIV-infected individuals has dropped with the advent of highly active antiretroviral therapy [5-8]. Other risk factors include long-term exposure to immunosuppressive therapy, particularly the use of methotrexate for autoimmune disease [9]. The presence of certain genetic variants, as well as environmental and occupational exposures, has also been linked with DLBCL, although these findings are still considered preliminary [10]. In terms of disease stage at presentation, about one-third of patients present with stage I or II disease (ie, disease confined to one side of the diaphragm); one-third present with bulky disease (>10 cm); about 40% present with extranodal involvement; and up to 20% present with bone marrow involvement [11].

The goal of the staging workup should be to identify all sites of disease and thus should include a thorough physical examination, blood tests, and imaging studies. Blood work should include complete blood counts, platelets, lactate dehydrogenase (LDH), comprehensive metabolic panel, and hepatitis B testing; HIV and other viral testing should be performed in selected cases. Other staging tests include multigated acquisition scan/echocardiogram if anthracyclines are indicated and pregnancy testing for women of childbearing age. A

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bone-marrow biopsy is not performed if bone-marrow involvement is indicated on PET/CT; conversely, if bone-marrow involvement is not indicated by PET/CT, then bone-marrow biopsy should be performed if relevant to clinical trial enrollment or management of the patient [12-15].

Lumbar puncture is indicated for involvement of the paranasal sinuses and testicles or for patients with disease at more than 2 extranodal sites with an elevated LDH or HIV-associated lymphoma. Diagnostic contrast-enhanced CT of the neck, chest, abdomen, and pelvis is considered the standard of care, and at present the Ann Arbor staging system is based on CT scan findings. PET/CT is increasingly being used for disease staging as well as treatment evaluation [16], with many patients undergoing both studies. Prospective and retrospective studies evaluating the efficacy of PET/CT for lymphoma staging suggest very good accuracy with the use of PET. In comparing 3 studies, PET upstaged disease in 8%–32% of cases when compared to conventional imaging. Disease was downstaged in 0%–15% of cases, and PET imaging resulted in a change in therapy for 8%–45% of cases, although whether these changes improved eventual outcome is unknown [17-19]. These data suggest that PET/CT should be routinely used for the evaluation of patients with DLBCL and has been recommended in the National Comprehensive Cancer Network guidelines [20]. The presence of B symptoms (fever >38º C, drenching night sweats, or unexplained loss of more than 10% of body weight within 6 months preceding diagnosis), performance status, and LDH levels have long been used to predict prognosis in patients with DLBCL as well as those with other forms of NHL.

However, it is worth noting that use of the suffix A or B in staging of DLBCL has recently been challenged by the Lugano Classification guidelines, based on the fact that it is not part of the International Prognostic Index (IPI) (see Appendix 1). The committee did suggest keeping it as a prognostic indicator while removing it from the Ann Arbor staging designation [13]. The IPI is a model developed in the pre-rituximab era based on 5 independent prognostic factors including age >60 years, Ann Arbor stage III–IV, LDH >1× normal, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, and more than 1 extranodal disease site. The IPI identifies 4 distinct prognostic groups: low-risk (0–1 factors), low-intermediate (2 factors), high-intermediate (3 factors), and high-risk (4–5 risk factors) with distinct outcomes for both failure-free survival and overall survival (OS) [21]. Its utility has been confirmed in many studies after the incorporation of rituximab [22-25]. A variant of the IPI, the revised-IPI (R-IPI), developed from a population-based registry within a single Canadian province, redistributes the 5 IPI elements into 3 prognostic outcome groups (P<0.001): very good (0 risk factors: 4-year progression-free survival [PFS] 94%, OS 94%), good (1–2 risk factors: 4-year PFS 80%, OS 79%), and poor (3–5 risk factors: 4-year PFS 53%, OS 55%) . Notably in the R-IPI, even the highest risk group had an OS >50% illustrating improvement in outcomes when treating with R-CHOP [26].

Since DLBCL is more common in older patients, an alternative index, the elder (E)-IPI, has been proposed [27], which uses an age cutoff of 70 years (rather than 60 years used in the IPI). The E-IPI was reported using the dataset from the US Intergroup E4494 trial [23] in which the median age was 70 years. In this study the R-IPI did not identify a very good risk group, thus minimizing its utility in patients >60 years. The E-IPI provided additional prognostic discrimination compared to the IPI between low and low-intermediate patients. Recently, the E-IPI has been validated using 2 other datasets of patients >60 years from the Groupe d'Etude de Lymphoma d'Adultes (GELA) 98.5 study and German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) RICOVER-60 [28].

The recognition of the complexity and heterogeneity of DLBCL has also led to numerous attempts at classification on the basis of gene-expression profile or immunophenotype. The gene-expression profile approach has revealed 3 major subgroups of DLBCL: germinal center B-cell-like (GCB), which has a gene-expression pattern that clusters with normal GCB and has a better outcome than the second subgroup, activated B-cell-like (ABC), which clusters with ABCs, and a third subtype, which consists of primary mediastinal lymphoma (PMBL) or entities that cannot be included in the other subtypes [29-32]. However, frozen material subjected to gene-expression profiling is difficult to reproduce and thus is of limited diagnostic value. Immunohistochemical profiling has been proposed as a surrogate for gene-expression profiling, with 2 studies finding the key markers to be expressions of BCL6, CD10, and MUM1/IRF4 [33,34].

Currently, immunophenotyping and genetic markers that should be considered for diagnosis should include CD20+, CD45+, CD3-, along with CD5 (CD5+ DLBCL), CD10 (GCB subtype), CD138 (plasmablastic differentiation), CD30 (which, depending on the rest of the panel, might indicate CD30+ DLBCL or PMBL or Hodgkin lymphoma), IRF/MUM1, BCL2, and BCL6. Other useful testing includes molecular cytogenetic and fluorescence *in situ* hybridization analyses. The importance of the *in situ* hybridization is underscored by the

recent discovery of "double-hit" lymphoma, an aggressive B-cell variant with a MYC breakpoint (at 8q24) and another break at BCL2. This double-hit genotype is present in 2%–12% of DLBCLs and is associated with a high proliferative index and poor outcome [35]. DLBCLs that are immunohistochemically double positive for MYC and BCL2 and/or BCL6 proteins are more common, carry a poorer prognosis, and may underlie the differences in outcome observed between ABC and GCB DLBCL [36,37].

Treatment Approaches

Disease stage, IPI score, the presence of B symptoms, and the size (bulk) of the disease are all essential factors to consider in the choice of therapy. Other factors to be considered in treatment choice include gene-expression profiles and immunohistochemical data, particularly immunophenotype.

The use of CHOP chemotherapy was established as the standard of care based on findings from a randomized study comparing CHOP with 3 other regimens: m-BACOD (low-dose methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone); ProMACE-CytaBOM (prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue); and MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin). CHOP was confirmed to be less toxic and equally effective as the other regimens [38]. In 2002, the GELA published results showing that adding rituximab to CHOP for patients older than 60 years improved both relapse-free survival and OS compared with CHOP alone [39]; similar results were found in the US Intergroup trial E 4494 [23]. These results were subsequently confirmed for patients younger than 60 years in the MabThera International Trial (MInT), in which patients were randomized to receive 6 cycles of CHOP-like therapy with or without rituximab; at a follow-up time of 3 years, both event-free survival (EFS) rates and OS rates were significantly better in the group given rituximab [25]. Updated results showed that the improvement in EFS and OS with rituximab persisted at a median 6 years of follow-up [40].

Although R-CHOP has been established as the standard of care, 3 other regimens should be noted. One of these regimens, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH), was developed by the U.S. National Cancer Institute in an attempt to overcome resistance by using continuous low-dose drug exposure. In one study of 69 patients with stage II–IV DLBCL, DA-EPOCH-R produced a complete response (CR) rate of 84% and, at a median follow-up interval of 5 years, an EFS rate of 75% (54% for those with high IPI scores) and an OS rate of 84%. Five patients (7%) developed grade 4 hematologic toxicity, and 10 (14%) developed neuropathy [41]. This regimen is currently being compared to R-CHOP in a trial led by the Cancer and Leukemia Group B.

The second regimen, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP), was recently compared to R-CHOP in a trial by the GELA group [42,43] for patients with low-risk to intermediate-risk IPI scores, this time adding rituximab. The trial showed that R-ACVBP produced better PFS rates (87%) and OS rates (92%) than R-CHOP (73% and 84%) but at the cost of high rates of serious adverse effects (42% versus 15%) [44]. Additionally, it is important to note that vindesine is not available in the United States.

The third regimen, evaluated by the DSHNHL, involved giving CHOP with etoposide (CHOEP) over either a 2-week or a 3-week period. The 2-week schedule was beneficial in terms of OS regardless of patient age, but etoposide was not beneficial for those over 60 and only slightly improved PFS in younger patients. It is worth noting that the superiority of CHOEP 21 was mitigated with the addition of rituximab. [45,46].

RICOVER-60, a study by DSHNHL, compared 6 cycles versus 8 cycles of CHOP-14 with and without rituximab. The trial found that 6 cycles R-CHOP-14 improved PFS and OS rates over CHOP-14 and confirmed no benefit to the use of more than 6 cycles of chemotherapy [47]. In addition, the schedule of R-CHOP administered every 2 versus 3 weeks has been tested in 2 randomized prospective trials and both failed to show an advantage of the q 2 week schedule [48,49] (see Appendix 2). Hence, the standard of care for DLBCL at this time is R-CHOP q 21 days, with the number of cycles depending on disease stage and IPI risk group.

Treatment of Limited (Stage I or II) DLBCL

The number of cycles of chemotherapy and the use of consolidation RT for limited-stage disease remain a matter of debate. The common practice is to add RT when using an abbreviated course of 3–4 cycles of R-CHOP for patients with low-risk disease as assessed by the IPI score; however, this approach should be used with caution as new knowledge becomes available on the importance of immunophenotypic, molecular, or cytogenetic markers in addition to IPI score to predict the risk of failure.

Use of Radiation for Limited DLBCL

Evidence in support of using RT for consolidation in DLBCL comes from 2 sources—the first is a group of 4 randomized trials conducted in the pre-rituximab era (see Appendix 3); and the second a group of 3 studies that included the use of rituximab including a large retrospective analysis, the MInT trial, and a recent update of the German UNFOLDER study.

The first trial to show a benefit from RT was the Southwest Oncology Group (SWOG) trial 8736 [50], in which patients with intermediate-risk or high-risk disease [stage I (bulky) or nonbulky stage II or II E disease (with only 1 extranodal site allowed)] received either 3 cycles of CHOP followed by RT to 40−55 Gy or 8 cycles of CHOP without RT. The combined therapy significantly improved the 5-year endpoints for both PFS (77% versus 64%, *P*=0.03) and OS (82% versus 72%, *P*=0.02). The PFS rate was higher for patients with 0 or 1 IPI risk factors (77%) than for those with 3 risk factors (34%). The CHOP-8 group had more life-threatening events, including ventricular dysfunction and cardiac death: 40% versus 30% in the CHOP-3+RT group. Updated results presented in abstract form showed that the OS curves crossed at 9 years, and the failure-free survival curves crossed at 7 years, with 15 relapses and deaths from lymphoma occurring in the CHOP-3+RT group between 5 and 10 years versus 8 in the CHOP-8 group. The difference in OS rates for stage-modified IPI groups (94% for those with favorable and no IPI risk factors versus 71% for those with 1 risk factor and 50% for 3 risk factors) led the authors to conclude that patients with worse risk factors may benefit from intense chemotherapy in terms of preventing late relapses [51]. However, another interpretation of these results is that RT cannot compensate for inadequate chemotherapy, thus patients who are to undergo abbreviated chemotherapy should be identified on the basis of risk factors and not on the potential use of consolidation RT.

The second of the trials to confirm the benefit of RT was ECOG 1484 [52], which compared outcomes after 8 cycles of CHOP with or without RT. Patients in this trial tended to have less favorable disease; more than two-thirds had stage II disease, and nearly half (166 of 352) had extranodal involvement. Patients who achieved a CR after chemotherapy were randomly assigned to receive RT to 30 Gy or observation; those with a partial response (PR) received 40 Gy. Despite the stringent design of this trial, more patients in the RT group had bulky disease. Six-year failure-free survival was superior in the combined modality arm (70% versus 53% with chemotherapy alone), and OS was also better (79% versus 67%), although the latter was not statistically significant in part due to limited sample size. The third of the pre-rituximab studies, GELA LNH 93-01, involved patients with stage I–II, mostly low-risk disease, and compared 3 cycles of CHOP plus RT with a much more aggressive regimen, dose-intensified ACVBP followed by methotrexate, etoposide, ifosphamide, and cytarabine. Not surprisingly, the aggressive regimen was found to be superior to CHOP-3 plus RT in terms of disease control (5-year EFS estimates 82% versus 74%, and OS 90% versus 81%); however, the toxicity of that regimen was considerable [53].

The fourth of the pre-rituximab trials, also conducted by the GELA, compared 4 cycles of CHOP with or without RT for older patients (>60), with stage I or II disease and no adverse factors; 65% of patients had stage I disease, 95% had an IPI score of 0, only 8% had bulky disease, and 50% had extranodal disease. At a median follow-up interval of 7 years, no differences in EFS or OS were noted between groups. Curiously, even though the population in this trial had fewer risk factors than those in the other 3 trials, the EFS rate was lower in this trial than that in the others, suggesting that the findings from this trial may not be applicable to those of others [54]. In addition to the lack of rituximab, other shortcomings limit the interpretation of these findings, such as the heterogeneity of patient characteristics and treatment; the fact that the choice of chemotherapy (abbreviated versus full-course) was made independently of the choice to use RT or not; and the use of outdated radiation doses, fields, and techniques (current standards of care are involved-site, to doses of 30–36 Gy, with 3-D conformal or intensity-modulated radiation therapy (IMRT).

The argument that the addition of rituximab negates the benefit of RT is undermined by the results of 2 studies, a retrospective review and the MInT trial. The former analysis from MD Anderson Cancer Center showed that adding RT improved both OS and PFS (5-year OS and PFS were 91% and 82% compared to 68% and 59%, respectively, for those who did not receive RT; *P*=0.0001) and also showed that this benefit was seen across all stages. Most of the patients in that study had received 6 or more cycles of R-CHOP. A matched pair analysis that was based on stage and accounted for number of R-CHOP cycles, receiving of RT, IPI score, tumor response to therapy, and disease bulk confirmed the benefit of RT in terms of longer OS and PFS (hazard ratios of 0.52 [OS] and 0.45 [PFS] for those who received RT). The MInT trial evaluated the benefit of adding rituximab to CHOP for patients with stage II–IV or bulky stage I DLBCL. R-CHOP was effective for patients with IPI=0 and without

bulky disease, for whom 3-year EFS rates were 90% (versus 74% for patients with IPI=1 and bulky disease). Notably, RT (30–40 Gy) was given to patients with primary extranodal involvement and bulky disease, and 50% of patients had some form of bulky disease (40% >7.5 cm). Rituximab minimized but did not eliminate the adverse prognostic effect of tumor bulk on outcome, thereby suggesting that RT would still have merit for patients with bulky disease [55].

In the UNFOLDER trial by the DSHNHL [56], 450 patients were randomized to receive either R-CHOP-14 versus R-CHOP-21 with randomization to radiation versus observation for patients with extranodal or bulky disease. The RT randomization was stopped when the second interim analysis showed a higher failure rate in the no-RT arms [57]. RICOVER-60, in a recently published analysis [47], looked at the benefit of radiation in elderly patients at all stages of disease, with radiation given to bulky and extralymphatic disease. In that report of 166 patients, the authors compared the best arm of immunochemotherapy (6 R-CHOP+2R) added to 36 Gy to initial bulky sites (≥7.5 cm) and compared to a cohort treated without radiation in an amendment of the RICOVER-60 trial in a prospective fashion. The addition of radiation showed statistically significant improvements in OS (90% for RT group versus 65% for no RT; P=0.001) and EFS (80% for RT group versus 54% for no RT; P=0.001), although the study was not a randomized study [47].

The standard of care in the United States is 3 or 4 cycles of R-CHOP plus RT (as described in the following section) for patients with limited-stage DLBCL with an IPI score of 0 or 1. In prospective phase II SWOG 0014, patients were treated with 3 cycles of R-CHOP plus involved-field radiation (40–46 Gy) in limited stage aggressive B-cell lymphoma with at least one adverse risk factor. When compared to the historic group from SWOG 8736, both 4-year PFS and OS showed a modest gain (88% and 92% compared to 78% and 88%, respectively) [58]. However, the choice of this abbreviated chemotherapy regimen must be made cautiously for patients with factors known to affect outcome other than stage and IPI score, such as bulky disease and/or aggressive pathology features. In such cases, 6 cycles of R-CHOP should be considered, to be followed by RT. The use of more aggressive chemotherapy regimens depending on the initial disease presentation must not preclude the use of radiation for consolidation if there is bulky disease. Although there is a paucity of data to support it, the addition of intrathecal chemotherapy prophylaxis, especially in extralymphatic craniofacial presentations, is highly considered in some academic centers. Ferreri et al [59], in a retrospective analysis of 200 adults with DLBCL treated with R-CHOP, concluded that the use of central nervous system (CNS) prophylaxis with high-dose methotrexate with or without intrathecal chemotherapy significantly reduced CNS failures in high-risk patients (involvement of specific extranodal sites and IPI index). On the other hand, in a recent analysis of 11 consecutive DSHNHL study trials, the addition of intrathecal prophylaxis with methotrexate did not affect the 2-year rate of CNS disease (4.2% compared to 2.3% in patients who did not receive intrathecal therapy, P=0.98) [60]. Therefore, the use of CNS prophylaxis remains an issue of debate and thus is administered according to institutional preference.

Radiation Dose and Fields for Limited LBCL

The radiation dose can be 30–40 Gy depending on the bulk of the disease and its response to chemotherapy. The impact of RT dose and other treatment-related and clinical factors on in-field control in stage I and II NHL was shown in a retrospective study by Kamath et al [61], where doses of 30 Gy in conjunction with chemotherapy (CHOP-based) were adequate with few in-field failures except in the setting of both bulky disease and an incomplete response to chemotherapy. In a prospective trial from the United Kingdom, patients with aggressive NHL (predominantly DLBCL) were randomized to receive RT to 40–45 Gy in 20–23 fractions or 30 Gy in 15 fractions. At a median follow-up time of 5.6 years, no differences were noted in overall response rate or in rate of within-field progression between the 2 dosage groups, suggesting that 30 Gy may be adequate for consolidative RT after chemotherapy for aggressive NHL [62]. With regard to radiation fields, involved-field RT (ie, that covers the initially involved and uninvolved adjacent disease sites) has been the current standard of care; however, evidence is emerging that smaller fields may be adequate [63], and a new set of field designs for involved-site radiation therapy (ISRT) has been developed and endorsed by the steering committee of the International Lymphoma Radiation Oncology Group [64,65]. These fields consider the findings from CT-based or PET/CT-based treatment planning and also incorporate 4-D treatment planning and image-guided treatment delivery. Details of clinical target volumes are forthcoming; in brief, the proposed guidelines for ISRT include treating only the sites of initial (pretherapy) involvement, excluding normal structures that were clearly uninvolved (including those that were displaced by the tumor). Determination of planning target volumes depends on estimated setup variations that are a function of the immobilization device, body site being treated, and image-

guidance system, if used. Every effort should be made to use modern radiation techniques for the delivery of consolidation RT, such as IMRT, proton therapy, 4-D CT simulation, CT-on-rails, and breath-hold techniques, which collectively can minimize the collateral radiation dose to the critical organs in the vicinity of the target.

Treatment of Advanced (Stage III or IV) DLBCL

R-CHOP 21 for 6 cycles is the standard of care in advanced DLBCL. The role of consolidative RT to bulky disease is supported by 2 post-rituximab trials, and a retrospective matched-pair analysis. The first of the 2 rituximab-era trials, MInT, indirectly addressed the role of RT and rituximab for patients with stage II–IV and bulky stage I DLBCL; RT was given to patients with primary extranodal involvement and bulky disease (30–40 Gy), and 50% of patients had some form of bulky disease (40% >7.5 cm). Patients with bulky disease tended to have poorer outcomes. However, because the MInT trial was not designed to evaluate the role of RT, its findings cannot directly address whether RT benefits patients with poor risk factors, and further analyses are planned. The other rituximab-era trial, RICOVER-60, compared 6 versus 8 cycles of biweekly CHOP-14 with and without rituximab for elderly patients, 54% of whom were also given RT (in all cases delivered to initial extranodal involvement and bulky disease [≥7.5 cm single or agglomerated masses]).

A preliminary comparison of results from 2 prospective trials of elderly patients by the DSHNHL [66] suggested that, in the rituximab era, patients with bulky disease had a superior EFS and PRS with RT; however, any advantage of giving RT to patients with bulky disease who achieved a confirmed or unconfirmed CR after 6 cycles of R-CHOP-14 needs to be further assessed in a randomized study. RICOVER-60, as mentioned earlier, included all stages of disease in elderly patients and showed that RT to bulky sites abrogates bulky disease as a risk factor and improves outcome of elderly patients with aggressive B-cell lymphoma.

The role of radiation in advanced stage has been addressed in single institutions' retrospective studies showing a benefit in the PFS and local control but not in the OS [67,68]. A multi-institutional retrospective analysis from the National Comprehensive Cancer Network outcome project showed that receipt of radiation improved both OS and freedom from failure for patients with stage III/IV disease (hazard ratios [HRs] 0.53 [*P*=0.07] and 0.77 [*P*=0.34]) [69].

Finally, a retrospective matched-pair analysis revealed a statistically significant benefit for OS and disease-free survival (DFS) from adding RT for patients with advanced stage DLBCL [70]. Notably, all patients in that study received more than 6 cycles of R-CHOP or equivalent chemotherapy, but relatively few of the matched pairs in the analysis had advanced stage disease. In conclusion, the use of RT in advanced disease at this point remains at the discretion of the treating physician, but in general it is used for sites that are bulky (>5 cm), did not achieve a CR, or are adjacent to critical organs (or were originally located in the vicinity of a critical organ, for instance the spine). In case RT is used, involved sites (described in the early stage) would be acceptable to use.

High-Dose Chemotherapy

Although high-dose chemotherapy has merit in relapsed patients, it is of unproven efficacy in an upfront approach according to a meta-analysis of 3,079 patients [71]. A number of randomized trials in the pre-rituximab era have been conducted to compare standard chemotherapy versus high-dose chemotherapy in unfavorable IPI score patients. The superiority of the use of high-dose chemotherapy could not be concluded [72,73]. In the rituximab era, Gruppo Italiano Terapie Innovative nei Linfomi [74], in a nonrandomized phase II trial, evaluated the feasibility of the approach and set the stage for the phase III study DLCL-04. In a randomized study by SWOG, 397 patients with age-adjusted classification of high-risk or high-intermediate risk were randomized after CHOP or R-CHOP to either 3 additional cycles of induction chemotherapy or autologous stem-cell transplantation. The latter was found to improve PFS but not OS. The authors attributed the lack of OS benefit to the effectiveness of salvage transplantation [75]. At present, stem-cell transplantation is not routinely used as a part of first-line therapy for patients DLBCL.

Use of Mid-Treatment PET in Predicting Outcome in Risk-Adapted Therapy

The potential predictive value of PET findings obtained during treatment with regard to outcome is being actively investigated. At this time, results are contradictory, with a large series [76,77] showing that interim PET can predict outcome; however, other series do not show such a conclusion [4]. ECOG E3404 addressed the reproducibility of reading the interim PET scan, with an agreement ranging from 68% to 71%. The investigators suggested the need for a standardized PET approach that needs to be considered for future studies and when making clinical decisions [78]. In a unique approach, investigators at Memorial Sloan Kettering compared

findings on interim PET scans with those on biopsy of the interim PET-positive lesions [79]. Only 5 of 37 patients with PET-positive scans had persistent disease in the biopsy sample; PFS rates were identical for patients with positive interim PET scans plus negative biopsy results and for those with negative interim PET scans [78]. Another retrospective study of 296 patients evaluated the association between interim PET scan response and outcome in 296 patients [80]. In that study, having a positive midterm PET scan predicted poorer PFS and OS at 5 years for all patients and for patients who received chemotherapy alone, but these differences lost significance when patients who received consolidation RT were considered separately. Finally, the presence of residual mass with a negative PET scan at the end of therapy has also been evaluated as a risk factor for relapse and as an indication to give consolidation RT, with one study finding that [81] a PET-negative residual mass >2 cm was associated with an inferior DFS and OS after chemotherapy alone. However, until further confirmatory studies become available, the use of PET/CT for predicting outcome should be considered investigational and should not influence clinical decisions.

Assessment of Response after Therapy

End-of-therapy assessment is to be performed using PET/CT, and the current recommendation is to grade the PET/CT using the 5-point Deauville scale (see Table 1). This 5-point scale uses the mediastinal blood pool as a comparator [82]. A score of 1 or 2 (in mid-therapy or end-of-therapy PET/CT) is considered to represent a CR, and a score of 3 is considered to predict a favorable outcome [4]. However, a score of 4 or 5 at the end of therapy is considered to be treatment failure; these patients should be considered for a biopsy to confirm the presence of residual disease before salvage therapy.

Table 1. 5-point Deauville Scale

• 1. No uptake
• 2. Uptake ≤ mediastinum
• 3. Uptake > mediastinum but ≤ liver
• 4. Uptake moderately higher than liver
• 5. Uptake markedly higher than liver and/or new lesions
• X. New areas of uptake unlikely to be related to lymphoma

Diagnosis and Treatment of Primary Mediastinal Lymphoma

PMBL is thought to originate from thymic B cells and is considered a separate entity in the World Health Organization classification. The presence of thymic lobules and Hassall corpuscles are indicative of thymic origin. Cells are usually sized medium to large, with strands of fibrosis present in the background. Expression of surface or cytoplasmic immunoglobulins is often absent; CD21 expression is typically absent, but CD30 is sometimes present in addition to CD19, CD20, and CD45. Chromosome 9p24 amplification is present in up to 50% of cases. The disease typically presents in the mediastinum in young people, and its histopathologic features usually help to confirm the diagnosis. Gene-expression profiling studies strongly support the relation between PMBL and classical Hodgkin lymphoma [30] and between PMBL and cases with borderline features known as "mediastinal gray zone lymphomas" [83]. PMBL often presents with a rapidly growing invasive tumor with contiguous spread, mostly confined to the thorax. Chest pain, cough, and dyspnea are common; pleural and pericardial effusions are also common.

The recommended treatment in the pre-rituximab era with the most promising outomes is chemotherapy, with MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) followed by radiation [84]. Other chemotherapy regimens evaluated have included CHOP, R-CHOP, VACOP-B (etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin), ProMACE-CytaBOM, and high-dose chemotherapy.

Retrospective studies have generally found that the use of RT following chemotherapy improves CR rates and EFS or PFS for patients with PMBCL. For example, a multicenter Italian study reported that consolidation RT with 30–36 Gy converted a large proportion of patients with gallium-positive disease to gallium-negative disease [84]. Similar results have also been reported with a higher rate of intrathoracic recurrences in patients who did not receive RT [85-88].

The optimal therapy for PMBL in the rituximab era is a subject of ongoing debate, with no accepted standard of care. A retrospective analysis of 63 patients in the modern era treated with R-CHOP, with or without radiation,

reported primary induction failure in 13 (21%) patients. The 5-year PFS and OS were 68% and 79%, respectively. These data demonstrate an unacceptably high rate of primary refractory disease on R-CHOP, particularly among patients with high-risk features that were not overcome despite RT. Treatment of PMBL with R-CHOP is associated with a high rate of primary refractory disease [89].

A recent report from the U.S. National Cancer Institute [90] showed that an infusional regimen dose-adjusted (DA) EPOCH-R (DA-EPOCH-R) resulted in excellent EFS (93%) and OS without RT at a median follow-up of 60 months. [90]. These results do challenge the role of RT in PMBL, however, as this was a fairly small phase II study; ideally the results need confirmation in a larger setting. Given mature data, however, this regimen has been incorporated in the 2014 National Comprehensive Cancer Network guidelines, although R-CHOP with consolidative RT remains a standard of care. An ongoing trial by the International Extranodal Lymphoma Study Group randomizes patients with normal PET scans after chemotherapy to adjuvant RT or no further treatment. This study should clarify the currently controversial role of RT following a CR to chemotherapy.

If RT is considered for PMBL, it should target the mediastinum and any positive lymph nodes in the neck or axilla, with care taken to avoid nearby critical organs such as the heart and lung. Use of modern radiation techniques is recommended, such as IMRT, proton therapy, breath-hold techniques, and onboard imaging. The clinical target volume should include the prechemotherapy volume in the superior-inferior dimension and the postchemotherapy volume in the transverse dimension into the lung. Inclusion of originally involved pericardial and pleural effusion is not advised because of the risk of excess toxicity to the heart or lungs. The planning target volume should include a daily setup margin, and the internal tumor volume should be determined on the basis of 4-D CT-based simulation. If a breath-hold technique is used in combination with daily onboard CT imaging, the breathing motion margin can be subtracted from the planning target volume. The recommended radiation dose is 30–36 Gy for patients with documented CR; in cases in which small residual low-activity masses are visible on PET/CT, a boost to 39.6 or 45 Gy can be used to target the area of concern.

Summary of Recommendations

- DLBCL is an aggressive lymphoma with treatment strategies dependent on staging, IPI score, gene-expression profile, and immunophenotyping markers at presentation.
- R-CHOP is the established standard of care based on multiple randomized trials showing superiority over CHOP alone.
- For favorable patients with IPI 0 or 1, especially those without bulk disease and adverse pathologic features, it is currently accepted to give an abbreviated course of immunochemotherapy followed by RT.
- The role of radiation was challenged in randomized trials in the pre-rituximab era, but recently prospective studies (UNFOLDER/RICOVER-60) and retrospective data have shown a potential benefit both for early and advanced stages.
- The fields and doses of radiation have been updated and entail the use of ISRT and modern technology including IMRT, motion-control techniques, and proton therapy. Also, radiation doses around 30 Gy are currently most commonly used in an effort to decrease acute and long-term side effects.
- The MinT study still shows a potential role for radiation in patients with bulky disease >7.5 cm.
- In patients with relapse or progressive disease, high-dose chemotherapy can be considered although no solid data support it being introduced as front-line therapy for patients with worse prognostic factors.
- Some studies suggest that interim PET/CT can predict outcome and thus allow for modifications of therapy (de-escalation or escalation); however, until further confirmatory studies become available, interim PET/CT should not influence clinical decisions.
- PMBL is successfully treated with R-CHOP combined with radiation or with DA-EPOCH-R, with radiation reserved for selected cases with residual positive disease.

Summary of Evidence

Of the 90 references cited in the *ACR Appropriateness Criteria® Diffuse Large B-Cell Lymphoma* document, 73 are categorized as therapeutic references including 29 well-designed studies and 22 good quality studies. Additionally, 17 references are categorized as diagnostic references including 1 well-designed study, 3 good quality studies, and 4 quality studies that may have design limitations. There are 31 references that may not be useful as primary evidence.

The 90 references cited in the *ACR Appropriateness Criteria® Diffuse Large B-Cell Lymphoma* document were published between 1993–2014.

While there are references that report on studies with design limitations, 55 well-designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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Appendix 1. International Prognostic Index

Standard IPI			
Number of Adverse Factors	**Risk Group**	**5-Year Disease-Free Survival Rate, %**	**5-Year Overall Survival Rate, %**
0 or 1	Low	70	73
2	Low-Intermediate	50	51
3	High-Intermediate	49	43
4 or 5	High	40	26
Revised IPI			
Number of Adverse Factors	**Risk Group**	**5-Year Disease-Free Survival Rate, %**	**5-Year Overall Survival Rate, %**
0	Very good	94	94
1 or 2	Good	80	79
3, 4, or 5	Poor	53	55

Negative IPI factors are: age >60 years, stage III/IV disease, elevated lactate dehydrogenase [LDH] level, Eastern Cooperative Oncology Group [ECOG] performance status ≥2, and more than one extranodal site of disease.

Appendix 2: Outcomes in Trials of Various Chemotherapy Regimens

Chemotherapy Comparison, Trial Name, and Reference	Number of Patients and Risk Group	Outcome	Treatment-Related Death or Other Side Effects
ACVBP versus 8 CHOP, GELA [43]	635 with ≥1 age-adjusted IPI risk factor (poor risk)	5-year-OS 46% ACVBP versus 38% CHOP	13% ACVBP versus 7% CHOP
ACVBP versus R-CHOP, LNH03-2B [44]	379; 358 had age-adjusted IPI 1, most with nonbulky disease	3-year OS 92% ACVBP versus 84% 8 R-CHOP	Grade 3–4 hematologic toxicity 38% ACVBP versus 9% R-CHOP
DA-EPOCH-R, NCI [41]	69 with stage II–IV disease	84% for those with low IPI, 54% for those with high IPI	
CHOP-14 versus CHOP-21 ± etoposide, DSHNHLB2 [45]	689>60 years	5-year OS 53% for CHOP-14 versus 41% for CHOP-21; 5-year EFS 44% for CHOP-14 versus 32.5% for CHOP-11	Infection 24% and mucositis 14% for CHOEP-14 versus 8% and 0% for CHOP-21
CHOP-14 versus CHOP-21 ± etoposide, DSHNHL [46]	710<61 years	CHOP-14 (±etoposide) led to improved OS in multivariate analysis	Infection 6.9% and mucositis 5.2% for CHOEP-14 versus infection 2.9% and mucositis 1.8% for CHOP-21; 20 second malignancies not correlated with any regimen

ACVBP = doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone**;** CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP = rituximab with CHOP; DA-EPOCH-R = dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; IPI = International Prognostic Index; EFS = event-free survival; OS = overall survival; CHOEP = CHOP with etoposide

Appendix 3: 4 Randomized Trials Characteristics

Trial Name and [Reference] No. of Patients Treatment Conditions	Stage (%)	Extra-nodal/ number of risk factors	Bulky (>10 cm)	Histology	Initial-Site Recurrence Within Field	Survival Estimates	Toxicity
SWOG 8736 [50] n=401 8 CHOP versus 3 CHOP + 40–55 Gy RT	Stage I (67%), bulky allowed; stage II (33%) nonbulky	37%/0 or 1 (71%–74%)	Not reported	24% follicular	Not available	5-year PFS 77%, CHOP-RT versus 64% CHOP; 5-year OS 82% CHOP-RT versus CHOP	Decreased LV 0% CHOP RT versus 7% CHOP; G4 neutropenia and 54% CHOP-RT versus 71% CHOP
ECOG 1484 [52] n=352 8 CHOP ± 30 Gy RT (40 Gy for patients with PR)	Stage II (2/3) No IPI	50%	31%	>80% DLBCL Follicular and Burkitt excluded	Patients with CR: failure 17/79 in RT and 31/93 in observed. Only 3 failure in initial sites in RT group versus 15 in observed.	5- year TTP 82% CHOP-RT versus 71% CHOP; 5- year OS 87%CHOP-RT versus 73% CHOP. PR patients converted to CR with RT had similar survival to CR patients	4 treated-related deaths, 2 congestive heart failure, and 32% G4 toxicity related to CHOP of the whole cohort
GELA <60 [53] n=630 ACVBP versus 3 CHOP + 40 Gy RT	Stage I (67%)	57%–53%	10%–12%	7% NK/anaplastic	Initial site: 23% in field and 41% out of field; out of field: 38% for chemo-RT and 72% for chemo alone	5-year EFS 82% versus 74%; 5-year OS 90% ACVBP versus 81% CHOP RT	16 deaths, 7 in ACVBP
GELA >60 [54] n=576 CHOP vs 4 CHOP + 40 Gy RT	Stage I (65%)	50%	8%	80% aggressive	21% in field in CHOP-RT and 47% initial site in CHOP alone	5-year EFS 61% in observed (NS); 5- year OS 72% in observed versus 68% in RT group (NS)	5 deaths related to chemo, G3 infection occurred in 3% in both groups

ACVBP = doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone**;** CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL = diffuse large B-cell lymphoma; RT = radiation therapy; CR = complete response; PR = partial response; IPI = International Prognostic Index; EFS = event-free survival; OS = overall survival; PFS = progression-free survival; NS = not stated; LV = left ventricular

Clinical Condition: **Diffuse Large B-Cell Lymphoma**

Variant 1: **Localized aggressive non-Hodgkin lymphoma. 30-year-old man with clinical stage IA DLBCL, presenting with 7-cm mass in the left axilla, with normal PS, normal LDH.**

Treatment	Rating	Comments
3 cycles R-CHOP followed by 30 Gy ISRT if PET-CR to chemotherapy	8	
4 cycles R-CHOP followed by 30 Gy ISRT if PET-CR	7	
6 cycles R-CHOP followed by 30 Gy ISRT if PET-CR to chemotherapy	6	
6 cycles R-CHOP alone	5	
6 cycles DA-EPOCH-R alone	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 2: **Localized aggressive non-Hodgkin lymphoma. 63-year-old woman presenting with DLBCL involving right maxillary sinus; largest dimension = 4.2 cm, right submandibular lymph nodes of 2 cm, stage IIEA, high LDH, IPI score = 2.**

Treatment	Rating	Comments
6 cycles R-CHOP plus 30–36 Gy ISRT	8	CNS prophylaxis may be used according to institution preference.
3–4 cycles R-CHOP plus 30–36 Gy ISRT	7	
6 cycles R-CHOP alone	3	
6 cycles DA-EPOCH-R alone	3	
6 cycles DA-EPOCH-R plus 30–36 Gy ISRT	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 3: **Localized aggressive non-Hodgkin lymphoma. 27-year-old woman with primary mediastinal lymphoma stage I, 11 cm in diameter, IPI = 1 (high LDH).**

Treatment	Rating	Comments
6 cycles R-CHOP followed by 36 Gy ISRT if PET-CR to chemotherapy	8	
6 cycles DA-EPOCH-R alone	7	
R-MACOP B Followed by 36–40 Gy ISRT	5	
6 cycles R-CHOP alone	3	
4 cycles R-CHOP followed by 36 Gy ISRT if PET-CR to chemotherapy	3	
6 cycles DA-EPOCH-R plus 36–40 Gy ISRT	2	ISRT may be used if there is biopsy-proven residual disease.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Diffuse Large B-Cell Lymphoma**

Variant 4: **Advanced aggressive non-Hodgkin lymphoma. 45-year-old patient with stage III DLBCL involving right supraclavicular area, mediastinal mass with paraspinal extension into the spinal cord, and para-aortic nodal region, IPI = 3.**

Treatment	Rating	Comments
6 cycles R-CHOP followed by 30–36 Gy ISRT to the paraspinal mass only	8	
6 cycles R-CHOP alone	6	
6 cycles DA-EPOCH-R alone	5	
6 cycles DA-EPOCH-R followed by ISRT only to paraspinal disease to 30–36 Gy	5	
6 cycles R-CHOP followed by 30–36 Gy ISRT to all initial sites of disease	3	
4 cycles R-CHOP followed by ISRT to 30–36 Gy to original sites of disease	3	
6 cycles of DA-EPOCH-R and ISRT to all original involved sites	3	
4 cycles R-CHOP followed by ISRT to all sites of disease to 45 Gy	2	
3 cycles R-CHOP followed by ISRT to all sites of disease to 45 Gy	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		