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DA-R-EPOCH vs R-CHOP in DLBCL: How Do We Choose?

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Abstract

The emerging molecular and prognostic characterization of diffuse large B-cell lymphoma (DLBCL) has challenged the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) treatment paradigm in recent years, with the identification of several DLBCL subtypes associated with significantly inferior survival after standard R-CHOP therapy. Efforts to improve upon the R-CHOP backbone have included dose intensification as well as the addition of new agents; the infusional dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) regimen has been identified as a potential replacement for R-CHOP in high-risk DLBCL. In this review, we provide a historical perspective on the R-CHOP and DA-R-EPOCH regimens and summarize the clinical trial literature regarding the efficacy of each regimen in various risk groups of DLBCL. Further, we propose clinical management scenarios in which DA-R-EPOCH may be preferred, including some for patient populations in which the use of R-CHOP vs DA-R-EPOCH is controversial.

Keywords

DA-R-EPOCH; diffuse large B-cell lymphoma (DLBCL); R-CHOP; R-EPOCH

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) in the United States. Treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemoimmunotherapy leads to a cure in 50% to 70% of patients.[1] R-CHOP has been the therapeutic standard for DLBCL for nearly 20 years, with the addition of rituximab to the CHOP backbone in the 2000s significantly improving survival after decades of unsuccessful efforts to intensify CHOP with additional chemotherapeutics. However, DLBCL is increasingly being recognized as a heterogeneous disease with distinct molecular subtypes affecting both response and survival. As such, intense interest has been shown in improving upon the standard-of-care R-CHOP regimen, particularly for patients with adverse prognostic features or high-risk tumor genetics. One

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Disclosures

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regimen in particular that has emerged is dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH), an intensified infusional variation of R-CHOP that has been studied in numerous DLBCL subtypes.[2] Herein, we review the history of the R-CHOP and DA-R-EPOCH regimens and summarize the literature regarding their efficacy in various risk groups of DLBCL, including potential patient populations in which DA-R-EPOCH may be preferred and those in which controversy persists.

Historical Perspective: Evolution of R-CHOP as the Standard of Care in DLBCL

Multiagent chemotherapy for DLBCL was pioneered by DeVita and colleagues in 1975 with the publication of a series of 27 patients who were treated with 6 cycles of procarbazine, vincristine, prednisone, and either cyclophosphamide or nitrogen mustard, with an overall response rate (ORR) of 70% and a complete response (CR) rate of 41%.[3] Long-term survival was demonstrated in the 37% of patients who were in remission 2 years after the completion of treatment, which the authors described as compatible with cure. These results were confirmed the following year in a randomized controlled trial by the Southwest Oncology Group of doxorubicin, vincristine, and prednisone (HOP) vs CHOP, which demonstrated a 1-year overall survival (OS) rate of 64% to 75%.[4] The possibility of curing aggressive B-cell lymphomas with chemotherapy alone had not previously been demonstrated in that era, and it generated considerable enthusiasm for the development of novel multiagent combination chemotherapy regimens.[5]

A series of intensified second- and third-generation regimens were developed in the 1980s, with the goal of improving response rates.[6,7] These regimens, which relied on an increased number of cytotoxic agents, included methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone (m-BA-COD); prednisone, doxorubicin, cyclophosphamide, and etoposide, followed by cytarabine, bleomycin, vincristine, and methotrexate with leucovorin rescue (ProMACE-CytaBOM); and methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B).[8] In several phase 2 trials, the CR rates with these regimens appeared significantly higher than those with first-generation regimens, such as CHOP,[9–11] with a doubling of historical OS rates.[12] Given the apparent superiority of these next-generation regimens in cross-trial comparisons, the Southwest Oncology Group and the Eastern Cooperative Oncology Group initiated a prospective, randomized phase 3 trial of CHOP, m-BA-COD, ProMACE-CytaBOM, and MACOP-B in 1986.[13] In this study of 899 patients with advanced-stage, intermediate- or high-grade NHL, no significant difference in ORR, CR rate, disease-free survival rate, or OS rate was found among any of the 4 regimens, with a 3-year OS rate of 54% for CHOP. However, the rates of grade 4 to 5 toxicities were significantly higher with m-BACOD and MACOP-B than with CHOP, and the third-generation regimens did not improve survival over CHOP in any of the prognostic subgroups. This landmark study established CHOP as the standard-of-care regimen for DLBCL because it was effective and conferred the least toxicity. The study also challenged the notion that “more is better” with respect to the chemotherapy-based management of DLBCL.

However, long-term cure rates were still relatively poor with CHOP, at less than 50%, particularly for adverse-risk subgroups identified by the International Prognostic Index (IPI) in 1993.[14] As such, calls were renewed for novel, non-chemotherapeutic approaches to the treatment of DLBCL, including monoclonal antibodies. The introduction of rituximab in a phase 1 study in 1994[15] quickly led to subsequent phase 2 studies that demonstrated considerable activity of rituximab as a single agent[16] and in combination with CHOP[17] in both untreated and relapsed DLBCL. R-CHOP was solidified as the new standard of care in DLBCL after the publication of several phase 3 trials, the first in 2002 by Coiffier and colleagues; in this study, 398 elderly patients aged 60 to 80 years with untreated DLBCL were treated with 8 cycles of CHOP vs R-CHOP.[18] The patients treated with R-CHOP had significantly higher rates of CR (76% vs 63%) and 2-year OS (70% vs 57%), with no significant differences in rates of adverse events between R-CHOP and CHOP. The superiority of R-CHOP in younger patients was confirmed in a study from the MabThera International Trial (MInT) Group published by Pfreundschuh and colleagues in 2006, in which 824 patients aged 18 to 60 years with DLBCL and a maximum IPI score of 1 were treated with 6 cycles of CHOP-like therapy vs rituximab plus CHOP-like therapy.[19] R-CHOP treatment resulted in significantly higher CR rates (86% vs 68%) and 3-year OS rates (93% vs 84%), with similar rates of toxicity. Long-term follow-up from both studies confirmed the superiority of R-CHOP and the ability to cure patients with this regimen, with 10-year OS rates of 44% vs 28% in elderly patients[20] and 6-year OS rates of 90% vs 80% in younger patients.[21] Several other studies have confirmed the survival advantage of R-CHOP over CHOP.[22,23]

Despite these high OS rates, R-CHOP is less effective at inducing short- and long-term remissions in some patients who have DLBCL, with approximately 20% of them having primary refractory disease and 30% subsequently experiencing relapse after achieving a complete remission.[1] Although previous attempts in the 1980s to improve the rates of response to the CHOP backbone via chemotherapy had been unsuccessful, the development of the infusional EPOCH regimen in the 1990s provided a novel and rational treatment paradigm that would challenge the R-CHOP status quo.

The Rationale and Development of Infusional DA-R-EPOCH in DLBCL

The development of the EPOCH regimen by the National Cancer Institute (NCI) began after in vitro studies of the individual components of CHOP chemotherapy found that less resistance to chemotherapy developed in tumor cells with prolonged low-concentration exposure to vincristine and doxorubicin than with short-duration bolus administration, and etoposide was found to be synergistic with CHOP.[2] With these data, a 96-hour continuous infusion regimen of EPOCH was designed that incorporated a dose-adjustment strategy based on the hematopoietic nadir to account for interpatient variations in steady-state plasma concentrations—hence the “dose-adjusted” nomenclature.[2]

EPOCH was first studied in 74 patients with relapsed or refractory low-, intermediate-, or high-grade NHL.[24] In the preliminary phase 2 report by Wilson and colleagues, published in 1993, patients with intermediate- or high-grade lymphoma had ORRs of 77% to 90%, with CRs in 20% to 42%. In a report published in 2000, the 8-year follow-up data for the

cohort demonstrated an ORR of 70% to 78% and a CR rate of 13% to 36% for patients with aggressive lymphomas.[25] At a median follow-up of 76 months, the OS was 12.6 months for patients with aggressive de novo lymphomas and 23.4 months for those with aggressive transformed lymphomas in the relapsed and refractory setting, with improved outcomes for EPOCH compared with other salvage regimens used at the time in cross-trial comparisons.

EPOCH was quickly brought into the front-line setting by 2002 in a phase 2 study of 50 patients with newly diagnosed DLBCL, which demonstrated an ORR of 100% and a CR rate of 92%, as well as an OS rate of 73% at a median follow-up of 62 months.[2] Subset analyses revealed no difference in response or survival rates according to IPI score, with an ORR of 100% in high-risk patients who had an IPI score of 3 to 5, but they revealed that overexpression of the BCL2 protein, a marker of the activated B-cell (ABC) subtype, was associated with inferior survival. The addition of rituximab to EPOCH was also examined in a phase 2 study by the NCI that was published in 2002, in which 38 patients with untreated or relapsed/refractory aggressive lymphomas received at least 6 cycles of DA-R-EPOCH.[26] The study cohort included a significant number of high-risk patients, with 61% of the untreated patients having at least high-intermediate IPI scores and 30% having a performance status of 2 or higher. The untreated patients had an ORR of 85% and a 1-year OS rate of 79%, which was encouraging given the preponderance of patients with high-risk IPI scores in the study. These early studies generated considerable enthusiasm for DA-R-EPOCH as a possible replacement for R-CHOP in DLBCL with a high-risk IPI score.

Improving Upon R-CHOP as the Standard of Care

The majority of phase 3 clinical trials for DLBCL over the past decade have focused on improving the R-CHOP backbone through treatment intensification or the addition of novel agents, including the use of precision medicine to determine which agents may be most appropriate for patients with specific molecular subtypes of DLBCL.

Intensifying Standard R-CHOP-21

Early research in the R-CHOP era, including the aforementioned MInT Group study, identified that patients with high IPI scores had an inferior response to standard R-CHOP. The MInT Group study found a significantly worse 3-year event-free survival (EFS) rate (76%) in patients with an IPI score of 1 and/or bulky disease than in those without these adverse characteristics (89%).[19] Given the prognostic validity of the IPI score in the rituximab era, with a 5-year OS rate of less than 50% for high-risk patients compared with a rate of more than 90% for low-risk patients,[27–29] extensive attempts have been made to intensify the standard 21-day R-CHOP (R-CHOP-21) regimen for patients with high-risk IPI scores.

Although most phase 3 intensification studies did not demonstrate improvements in survival over R-CHOP-21 (Table 1), limited evidence suggests that treatment intensification can improve survival in very select populations. In a randomized trial conducted by the French Groupe d'Etude des Lymphomes de l'Adulte, which compared rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) vs R-CHOP, an OS

benefit was observed in patients aged 18 to 59 years with an age-adjusted IPI score of 1 who were treated with R-ACVBP, with 3-year OS rates of 92% vs 84%.[30] However, the trial evaluated a very narrow patient population, and the rates of short- and long-term toxicities were higher in the R-ACVBP arm, with a 38% rate of febrile neutropenia (vs 9% in the R-CHOP group) and an increase in secondary malignancies.[31] Further post hoc analysis of this study revealed that R-ACVBP was superior to R-CHOP only in patients with the non-germinal center B-cell (non-GCB) subtype of DLBCL.[32]

The limited toxicity and extended anti-lymphoma activity of rituximab were the focus of several studies to intensify rituximab administration with R-CHOP, including several phase 2 trials of dose-dense rituximab with R-CHOP that suggested improved survival in elderly patients with a poor prognosis.[45,46] However, subsequent randomized phase 3 data on R-CHOP with weekly rituximab found no difference in survival with intensified rituximab and greater toxicity in older patients. Overall, the intensification of standard R-CHOP-21 to treat DLBCL in both unselected patients and those with high-risk IPI scores has been unsuccessful in improving outcomes.

Precision Medicine and R-CHOP: the XR-CHOP Paradigm

Given the limited success in improving R-CHOP outcomes by means of classic risk stratification with the IPI score, intense interest is being shown in designing new treatment regimens based on specific subtypes of DLBCL, moving toward the use of precision medicine in lymphoma. Gene expression profiling has demonstrated 2 distinct subtypes of DLBCL based on the cell from which the lymphoma originated during the process of B-cell differentiation: germinal center B-cell (GCB) lymphoma and activated B-cell (ABC) lymphoma.[47] The prognosis for ABC DLBCL is significantly worse than that for GCB DLBCL after R-CHOP treatment, with 5-year OS rates of 45% to 56% in the ABC subtype vs 78% to 80% in the GCB subtype.[48] Further, there are molecular subtypes of DLBCL, which also confer a worse prognosis. In the latest World Health Organization (WHO) guidelines, the entity “high-grade B-cell lymphoma” refers to the identification of *MYC*, *BCL2*, and *BCL6* rearrangements by fluorescence in situ hybridization (FISH), with the presence of *MYC* and *BCL2* or *BCL6* rearrangements referred to as “double-hit lymphoma” (DHL) and the presence of all 3 rearrangements referred to as “triple-hit lymphoma” (THL).[49] In large retrospective series, both DHL and THL confer a very poor prognosis when treated with standard R-CHOP therapy, with 5-year OS rates of 22% to 27%.[49] Lymphomas that co-express MYC and BCL2 proteins by immunohistochemistry without underlying rearrangements, colloquially termed “double-expressor lymphomas” (DELs), are also an adverse prognostic group with an inferior 5-year OS rate of 30% to 36% when treated with R-CHOP.[49]

Given these inferior outcomes, recent trials have focused on developing novel regimens that are based on the cell of origin or molecular subtype of DLBCL, often by using an “XR-CHOP’ framework in which a new therapeutic (“X”) is added to the R-CHOP backbone.[50,51] As shown in Table 1, these phase 3 studies have also had limited success, with no improvement in survival for the non-GCB/ABC subtype of DLBCL after the addition of bortezomib, lenalidomide (Revlimid, Celgene), or ibrutinib (Imbruvica,

Pharmacyclics/Janssen) to R-CHOP. Other novel agents are in development and have shown promising activity; for example, the BCL2 inhibitor venetoclax (Venclexta, AbbVie) was added to R-CHOP in a recently reported phase 2 study in which 28% of patients had ABC DLBCL.[52]

Challenging R-CHOP With DA-R-EPOCH to Create a New Standard of Care

Given the limited success of R-CHOP intensification and XR-CHOP in improving outcomes for patients who have DLBCL with high-risk clinical and molecular features, DA-R-EPOCH has emerged as a potential new treatment backbone, with numerous studies conducted over the past decade.[26,53–60] These trials have been primarily in the phase 2 setting and have focused on the use of DA-R-EPOCH in specific high-risk DLBCL cohorts (see eTable at www.hematologyandoncology.net).

Clinical and Biological Scenarios in Which DA-R-EPOCH Is Preferred

High-Grade B-Cell Lymphoma With DHL/THL.—Informed by several retrospective studies demonstrating better outcomes with intensified therapy in patients having high-grade DLBCL with rearrangements indicating a poor prognosis,[61,62] a phase 2 trial evaluating DA-R-EPOCH in patients with *MYC*-rearranged DLBCL was conducted by the NCI.[63] At a median follow-up of 14 months for the first 52 patients, the progression-free survival (PFS) rate was 79% for the whole cohort and 87% for patients with DHL, which were promisingly high survival rates with DA-R-EPOCH. However, not all patients in the trial had DHL, and some patients had Burkitt lymphoma. A subsequent meta-analysis of R-CHOP vs dose-intensive therapies in DHL, which included 11 retrospective analyses but no randomized controlled studies, found a significantly longer PFS but not OS in patients with DHL treated with frontline DA-R-EPOCH than in those treated with R-CHOP.[64] The final results of the aforementioned NCI phase 2 study were published in 2018 and demonstrated a 4-year OS of 77% for all patients who had *MYC*-rearranged DLBCL treated with DA-R-EPOCH.[53] Of the 53 patients in the final analysis, 45% had DHL, and the 4-year OS rate of the patients who had DHL was 82%, with a 4-year OS rate of 72% in the patients who had DHL with high IPI scores of 3 to 5. Although this was a phase 2 single-arm study, it demonstrated the highest long-term survival rates of patients with high-risk DHL in the modern era and led to the inclusion of DA-R-EPOCH in the National Comprehensive Cancer Network (NCCN) guidelines. However, a recent large retrospective review of more than 6800 patients with *MYC*-rearranged DLBCL, DHL, or THL who were treated with R-CHOP or DA-R-EPOCH demonstrated no difference in 4-year OS between the 2 regimens.[65] Overall, the evidence for the efficacy of DA-R-EPOCH in DHL/THL is limited, but it is frequently administered at lymphoma centers owing to the known poor outcomes with standard R-CHOP.

Primary Mediastinal B-Cell Lymphoma.—Primary mediastinal B-cell lymphoma (PMBL) is a rare subtype of NHL that was previously thought to be a subtype of DLBCL, although it has now been recognized as a unique disease that shares some features with Hodgkin lymphoma.[66] R-CHOP has historically been the mainstay of therapy, with 3-year EFS rates of 78%[67] and 5-year OS rates of 82%,[68] and it is frequently combined with consolidative radiation. Given that PMBL is more common in young women such that

secondary breast cancers and long-term cardiovascular toxicity from mediastinal radiation are of concern, DA-R-EPOCH without consolidative radiation has been explored as a potential therapeutic approach. In a landmark phase 2 study by the NCI in 2013, 51 patients with untreated PMBL received 6 to 8 cycles of DA-R-EPOCH without radiation, with a 5-year EFS rate of 93% and a 5-year OS rate of 97%.[54] Given these very high survival rates, DA-R-EPOCH is commonly used to treat PMBL, although 6 cycles of R-CHOP followed by consolidative involved-field radiation therapy is also reasonable if the risks of mediastinal radiation are accepted.[69,70]

HIV-Associated DLBCL.—Most patients with HIV-associated NHL have advanced-stage DLBCL or Burkitt lymphoma, and their prognosis is poor compared with that of HIV-negative patients; their median survival was 5 to 6 months in the pre-antiretroviral therapy (ART) era and is approximately 2 years with CHOP chemotherapy.[71] However, the risk for treatment-related mortality was significantly higher with the addition of rituximab to CHOP than with CHOP alone in a phase 3 randomized trial in 2005, particularly in patients with a CD4 cell count of less than 50/μL.[72] This finding significantly dampened interest in R-CHOP for the treatment of HIV-associated DLBCL, and EPOCH was therefore explored for these patients, with a trial in 2003 demonstrating an OS rate of 60% for EPOCH at a median follow-up of 53 months.[73] Subsequent studies found that outcomes for HIV-associated NHL were significantly improved in the era of ART and that rituximab could be safely given concurrently with ART to improve survival.[71] A landmark phase 2 randomized study in 2010 by Sparano and colleagues administered EPOCH with either concurrent or sequential rituximab to 106 patients with untreated HIV-associated aggressive lymphoma; the 2-year OS rate was 70% with concurrent DA-R-EPOCH, and 70% to 75% of the surviving patients were without evidence of progressive lymphoma at 2 years.[55] Notably, the rate of treatment-associated deaths was 7.3% to 9.8% in the study, lower than the 14% in the aforementioned R-CHOP vs CHOP study. A subsequent analysis of pooled data from 1546 individual patients in 19 prospective clinical trials of HIV-associated NHL found a significantly improved OS with EPOCH compared with CHOP, although the difference in OS was of only borderline significance when DA-R-EPOCH was compared with R-CHOP (P=.087).[74] In the absence of robust randomized data, many centers utilize DA-R-EPOCH for HIV-associated DLBCL, and it is the preferred regimen in the NCCN guidelines, particularly for patients with other adverse risk factors, such as a high IPI score, DEL, or DHL. However, R-CHOP is also a reasonable therapeutic choice.

Gray Zone Lymphoma.—Gray zone lymphoma (GZL) is a very rare and distinct lymphoma having pathologic features of both DLBCL and classic Hodgkin lymphoma (cHL), with a more aggressive presentation and inferior outcomes in comparison with DLBCL and cHL.[75,76] Although GZL has historically been treated with both DLBCL and cHL paradigms, outcomes are superior when it is treated with R-CHOP or DA-R-EPOCH, for which the 2-year PFS rate is 52%, compared with 22% for cHL-type therapy.[77] A prospective study of DA-R-EPOCH in 24 patients with untreated mediastinal GZL found a 3-year EFS rate of 62% and a 3-year OS of 74%,[56] which are better than historical survival rates[78] and have led to the use of DA-R-EPOCH for GZL.

Clinical and Biologic Scenarios in Which DA-R-EPOCH vs R-CHOP Is Controversial

Patients With High-Risk IPI Scores.—With data from the initial studies and an observational study in 2007[79] suggesting that DA-R-EPOCH may have particular activity in patients who have high-risk IPI scores, a phase 2 study of DA-R-EPOCH in 72 patients with untreated stage II or higher DLBCL was published by the NCI in 2008.[57] The authors of this landmark study included per protocol assessments of the expression of several biomarkers, including CD10, BCL6, and MUM1, to determine GCB or ABC subtype, as well as the expression of BCL2, given the inferior survival with DA-R-EPOCH in their previous 2002 study.[2] The study cohort included a substantial proportion of high-risk patients, with 40% of them having an IPI score of 3 or higher. The CR rates were 100% in patients with low IPI scores (0–2) and 82% in those with high IPI scores (3–5), with a lower 5-year survival rate of 74% in the patients with an IPI score of 3 and 37% in those with an IPI score of 4 or 5, compared with 90% to 100% in those with an IPI score of 0 to 2. A difference of borderline significance was found between the 5-year OS rates of patients with GCB and those with ABC DLBCL (P=.059), although the difference in 5-year PFS was not significant. The authors concluded that DA-R-EPOCH may be more effective than R-CHOP for patients with GCB DLBCL as well as for patients with an IPI score of 0 to 2, and they also stated that the lower survival rate of the patients with high IPI scores was due to 4 deaths without progression. However, it is important to note that historical 5-year OS rates in the R-CHOP era were 67% for those with an IPI score of 3 and 54% for those with an IPI score of 4 or 5,[80] so DA-R-EPOCH was not associated with a significant improvement in these patients with high-risk IPI scores.

However, subsequent studies in HIV-associated DLBCL and *MYC*-rearranged DLBCL, which enrolled large proportions of patients with high IPI scores, generated renewed interest in evaluating DA-R-EPOCH for patients with high-risk IPI scores. A phase 2 study by the Spanish PETHEMA Group evaluated 81 patients with untreated, poor-risk DLBCL, 86% of whom had high-risk IPI scores of 3 to 5.[58] The CR rate was 80% and the 10-year OS rate was 64%, with no significant difference in survival on the basis of IPI score or GCB vs ABC subtype. Toxicity was as previously described with DA-R-EPOCH; an episode of neutropenic fever developed in 46% of the patients, although 91% received all planned cycles. The 10-year OS rate in this study of patients with high-risk IPI scores was the highest described in the literature at the time, supporting further evaluation.

The Intergroup phase 3 randomized study of R-CHOP vs DA-R-EPOCH for untreated DLBCL enrolled 524 patients over an 8-year period from 2005 to 2013.[59] A total of 491 eligible patients were randomly assigned to 6 cycles of either R-CHOP or DA-R-EPOCH. Most patients had advanced-stage disease, although the proportion of enrolled patients with a high-risk IPI score was much smaller than in previous studies of DA-R-EPOCH; 25% of the patients had an IPI score of 3, and 12% had an IPI score of 4 or 5. Evaluating for DHL or DEL was not prospectively required, and only a minority of patients were subsequently found to have either DEL (16%) or DHL (3 patients). At a median follow-up of 5.2 years, no significant differences were found in response rates or survival rates between the R-CHOP or DA-R-EPOCH cohorts; the 5-year OS rates were 79% for R-CHOP and 78% for DA-R-EPOCH. Post hoc subgroup analyses revealed a significantly higher PFS rate in

the patients in the DA-R-EPOCH group with an IPI score of 3 to 5 without a significant difference in OS. No other subgroup differences in survival were noted between the patients who received R-CHOP and those who received DA-R-EPOCH, including no difference for the patients with DEL. Toxicity was significantly worse with DA-R-EPOCH; grade 3 to 5 adverse events developed in 98% of patients in the DA-R-EPOCH arm vs 78% in the R-CHOP arm. Although the efficacy of R-CHOP and DA-R-EPOCH did not differ in this study, there are concerns that the study cohort overrepresented favorable-risk patients, which may have obscured any benefit of DA-R-EPOCH. This is evidenced by a 3-year PFS rate in the control arm of 72%, which is higher than expected, as well as a lower number of patients with DEL in the study than expected and very few patients with DHL/THL. An initial requirement of fresh frozen tissue for study enrollment may have exacerbated this selection bias because patients with high-risk disease, for whom rapid progression is a concern, were likely not enrolled owing to an urgent need for the initiation of treatment.

As such, R-CHOP has remained the standard for the unselected frontline treatment of patients with DLBCL, including those with high-risk IPI scores, the aforementioned phase 3 study having been unable to answer questions about the utility of DA-R-EPOCH in DEL or DHL/THL owing to low patient numbers.

Activated B-Cell Subtype DLBCL.—Given the poor prognosis of patients with ABC DLBCL, several studies have focused on evaluating the DA-R-EPOCH platform specifically for this subtype. On the basis of a greater understanding of *CARD11* and *MYD88* mutations in ABC DLBCL, the NCI added bortezomib to EPOCH without rituximab in 49 patients with relapsed DLBCL and found a significantly higher response rate and median OS in those who had ABC DLBCL than in those who had GCB DLBCL with the addition of bortezomib.[81] However, subsequent phase 2 studies have diminished enthusiasm for DA-R-EPOCH in ABC DLBCL,[53] such as the Cancer and Leukemia Group B (CALGB) study of 69 patients with untreated DLBCL that included an assessment of cell of origin.[60] In that study, 51% of the patients had non-GCB/ABC DLBCL, and time to progression, EFS, and OS were all significantly worse in non-GCB than in GCB DLBCL after treatment with DA-R-EPOCH. Subsequent research on the management of ABC DLBCL has shifted to novel agents in an XR-CHOP platform, as detailed in Table 1.

Double-Expressor Lymphoma.—As previously outlined, the phase 3 NCI-sponsored study of R-CHOP vs DA-R-EPOCH did not demonstrate a difference in survival for patients with DEL, although this conclusion was made in a post hoc subgroup analysis in a study that included very few patients with DEL.[59] Retrospective analyses have confirmed this finding,[82,83] and as such, R-CHOP has remained the standard of care for DEL.

Richter Syndrome.—The most common histology in patients with Richter syndrome is DLBCL. The prognosis for patients with Richter syndrome is extremely poor, with a median OS of 9 months in the modern era.[84] R-CHOP is most commonly used for these patients, and retrospective analyses have suggested that DA-R-EPOCH does not significantly improve outcomes and may be associated with worse toxicity, with 73% of patients experiencing an adverse event in the first cycle and 30% dying without progression of lymphoma in one study of 46 patients.[85] However, preliminary results of a phase 2 trial of venetoclax plus

DA-R-EPOCH for Richter syndrome found a median OS of 16.3 months in 27 patients, and more data are needed.[86]

Testicular DLBCL.—Primary testicular lymphoma, which is histologically DLBCL in the majority of cases, is a rare extranodal NHL that has inferior OS compared with nodal DLBCL, with no plateau in survival curves and continual late relapses for more than 10 years after diagnosis.[87,88] The current standard of care for patients with limited-stage disease involves orchiectomy, 6 cycles of R-CHOP, central nervous system (CNS) prophylaxis (given the high risk for CNS relapse), and contralateral scrotal radiation therapy to prevent contralateral testicular recurrence.[89] None of the retrospective series of patients who had testicular DLBCL treated with intensified regimens such as DA-R-EPOCH have demonstrated an advantage over R-CHOP.[90]

Current Landscape of DLBCL Management

Despite intensive study over the past 40 years and the identification of novel subtypes of disease with adverse risk factors, the management of DLBCL has remained relatively unchanged in the R-CHOP era, with standard R-CHOP effecting a cure in the majority of patients. Although intensified treatment with DA-R-EPOCH is another treatment option studied in some subtypes of DLBCL, the recent negative phase 3 trial of R-CHOP vs DA-R-EPOCH in the frontline setting has solidified the position of R-CHOP as the therapeutic standard and has unfortunately left several questions unanswered regarding high-risk subsets such as DEL and DHL/THL. DA-R-EPOCH is also more costly and more toxic than R-CHOP,[91] features that further call into question its utility for most patients with DLBCL. The evidence-based use of R-CHOP vs DA-R-EPOCH for various subtypes of DLBCL is summarized in Table 2, with phase 2 single-arm studies in DHL/THL, PMBL, HIV-associated DLBCL, and GZL suggesting that DA-R-EPOCH can be used. It is important to note that considerable controversy surrounds these data, as most of the trials included unselected patients with DLBCL and lacked a comparator arm or had inadequate power to evaluate efficacy in specific high-risk subsets. Further, time-dependent selection bias in clinical trials, in which patients with aggressive presentations cannot be enrolled owing to trial requirements for tissue biopsies or cell of origin testing, may skew data.[92,93] As such, standard R-CHOP is an appropriate alternative in all of these scenarios, particularly for patients who are unlikely to be able to tolerate more intensive and toxic DA-R-EPOCH.

Complicating the selection of an initial treatment for DLBCL is the emerging evidence of molecular heterogeneity in this disease. Although cell of origin provided initial insight, currently at least 8 groups of molecularly distinct subsets in DLBCL are known,[94] increasing our appreciation of pathogenic heterogeneity.[95,96] Further, the effect of *TP53* mutations on treatment choice is undergoing active study, as *TP53* mutations are independently associated with inferior outcomes of treatment with R-CHOP, but not DA-R-EPOCH.[97] Studies to address these gaps in the literature are urgently needed, and numerous trials are in progress evaluating additions to the DA-R-EPOCH backbone, including lenalidomide plus DA-R-EPOCH in DHL and DEL,[98] venetoclax plus DA-R-EPOCH in aggressive NHL,[99] and acalabrutinib (Calquence, AstraZeneca) with either R-CHOP or DA-R-EPOCH in DLBCL.[100] Enrollment in clinical trials is paramount for patients who

have DLBCL with adverse clinical or pathologic features, particularly trials of novel agents with robust biological rationales.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do? Hematology (Am Soc Hematol Educ Program). 2016;2016(1):366–378. [PubMed: 27913503]
2. Wilson WH, Grossbard ML, Pittaluga S, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood. 2002;99(8):2685–2693. [PubMed: 11929754]
3. DeVita VT Jr, Canellos GP, Chabner B, Schein P, Hubbard SP, Young RC. Advanced diffuse histiocytic lymphoma, a potentially curable disease. Lancet. 1975;1(7901):248–250. [PubMed: 46388]
4. McKelvey EM, Gottlieb JA, Wilson HE, et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer. 1976;38(4):1484–1493. [PubMed: 791473]
5. Wilson WH. Drug resistance in diffuse large B-cell lymphoma. Semin Hematol. 2006;43(4):230–239. [PubMed: 17027657]
6. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep. 1979;63(11–12):1727–1733. [PubMed: 526911]
7. Goldie JH, Coldman AJ, Gudauskas GA. Rationale for the use of alternating non-cross-resistant chemotherapy. Cancer Treat Rep. 1982;66(3):439–449. [PubMed: 7060033]
8. Miller TP, Dana BW, Weick JK, et al. Southwest Oncology Group clinical trials for intermediate- and high-grade non-Hodgkin's lymphomas. Semin Hematol. 1988;25(2)(suppl 2):17–22. [PubMed: 2456619]
9. Shipp MA, Harrington DP, Klatt MM, et al. Identification of major prognostic subgroups of patients with large-cell lymphoma treated with m-BACOD or M-BACOD. Ann Intern Med. 1986;104(6):757–765. [PubMed: 2422995]
10. Fisher RI, Longo DL, DeVita VT Jr, Hubbard SM, Miller TP, Young RC. Long-term follow-up of ProMACE-CytaBOM in non-Hodgkin's lymphomas. Ann Oncol. 1991;2(suppl 1):33–35.
11. Klimo P, Connors JM. MACOP-B chemotherapy for the treatment of diffuse large-cell lymphoma. Ann Intern Med. 1985;102(5):596–602. [PubMed: 2580468]
12. Fisher RI. Diffuse large-cell lymphoma. Ann Oncol. 2000;11(suppl 1):29–33.
13. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med. 1993;328(14):1002–1006. [PubMed: 7680764]
14. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329(14):987–994. [PubMed: 8141877]
15. Maloney DG, Liles TM, Czerwinski DK, et al. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Blood. 1994;84(8):2457–2466. [PubMed: 7522629]
16. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood. 1998;92(6):1927–1932. [PubMed: 9731049]
17. Vose JM, Link BK, Grossbard ML, et al. Phase II study of rituximab in combination with chop chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2001;19(2):389–397. [PubMed: 11208830]
18. Coiffier B, Lepage E, Brière J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235–242. [PubMed: 11807147]

19. Pfreundschuh M, Trümper L, Österborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7(5):379–391. [PubMed: 16648042]
20. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010;116(12):2040–2045. [PubMed: 20548096]
21. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011;12(11):1013–1022. [PubMed: 21940214]
22. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006;24(19):3121–3127. [PubMed: 16754935]
23. Sehn LH, Donaldson J, Chhanabhai M, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol. 2005;23(22):5027–5033. [PubMed: 15955905]
24. Wilson WH, Bryant G, Bates S, et al. EPOCH chemotherapy: toxicity and efficacy in relapsed and refractory non-Hodgkin's lymphoma. J Clin Oncol. 1993;11(8):1573–1582. [PubMed: 7687667]
25. Gutierrez M, Chabner BA, Pearson D, et al. Role of a doxorubicin-containing regimen in relapsed and resistant lymphomas: an 8-year follow-up study of EPOCH. J Clin Oncol. 2000;18(21):3633–3642. [PubMed: 11054436]
26. Wilson WH, Gutierrez M, O'Connor P, et al. The role of rituximab and chemotherapy in aggressive B-cell lymphoma: a preliminary report of dose-adjusted EPOCH-R. Semin Oncol. 2002;29(1):41–47.
27. Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(14):2373–2380. [PubMed: 20385988]
28. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109(5):1857–1861. [PubMed: 17105812]
29. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood. 2014;123(6):837–842. [PubMed: 24264230]
30. Récher C, Coiffier B, Haioun C, et al. ; Groupe d'Etude des Lymphomes de l'Adulte. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03–2B): an open-label randomised phase 3 trial. Lancet. 2011;378(9806):1858–1867. [PubMed: 22118442]
31. André M, Mounier N, Leleu X, et al. ; Groupe D'Etude Des Lymphomes De L'Adulte. Second cancers and late toxicities after treatment of aggressive non-Hodgkin lymphoma with the ACVBP regimen: a GELA cohort study on 2837 patients. Blood. 2004;103(4):1222–1228. [PubMed: 14576060]
32. Molina TJ, Canioni D, Copie-Bergman C, et al. Young patients with non-germinal center B-cell-like diffuse large B-cell lymphoma benefit from intensified chemotherapy with ACVBP plus rituximab compared with CHOP plus rituximab: analysis of data from the Groupe d'Etudes des Lymphomes de l'Adulte/lymphoma study association phase III trial LNH 03–2B. J Clin Oncol. 2014;32(35):3996–4003. [PubMed: 25385729]
33. Pfreundschuh M, Schubert J, Ziepert M, et al. ; German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol. 2008;9(2):105–116. [PubMed: 18226581]
34. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03–6B study): a randomised phase 3 trial. Lancet Oncol. 2013;14(6):525–533. [PubMed: 23578722]

35. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet. 2013;381(9880):1817–1826. [PubMed: 23615461]
36. Chiappella A, Martelli M, Angelucci E, et al. Rituximab-dose-dense chemotherapy with or without high-dose chemotherapy plus autologous stem-cell transplantation in high-risk diffuse large B-cell lymphoma (DLCL04): final results of a multicentre, open-label, randomised, controlled, phase 3 study. Lancet Oncol. 2017;18(8):1076–1088. [PubMed: 28668386]
37. Vitolo U, Trnený M, Belada D, et al. Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. J Clin Oncol. 2017;35(31):3529–3537. [PubMed: 28796588]
38. Lugtenburg PJ, de Nully Brown P, van der Holt B, et al. Rituximab-CHOP with early rituximab intensification for diffuse large b-cell lymphoma: a randomized phase III trial of the HOVON and the Nordic Lymphoma Group (HOVON-84). J Clin Oncol. 2020;38(29):3377–3387. [PubMed: 32730183]
39. Ohmachi K, Kinoshita T, Tobinai K, et al. ; Japan Clinical Oncology Group. A randomized phase 2/3 study of R-CHOP vs CHOP combined with dose-dense rituximab for DLBCL: the JCOG0601 trial. Blood Adv. 2021;5(4):984–993. [PubMed: 33591324]
40. Seymour JF, Pfreundschuh M, Trněný M, et al. R-CHOP with or without bevacizumab in patients with previously untreated diffuse large B-cell lymphoma: final MAIN study outcomes. Haematologica. 2014;99(8):1343–1349. [PubMed: 24895339]
41. Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2017;35(22):2473–2481. [PubMed: 28426350]
42. Davies A, Cummin TE, Barrans S, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20(5):649–662. [PubMed: 30948276]
43. Younes A, Sehn LH, Johnson P, et al. ; PHOENIX investigators. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. J Clin Oncol. 2019;37(15):1285–1295. [PubMed: 30901302]
44. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: A phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. J Clin Oncol. 2021;39(12):1317–1328. [PubMed: 33621109]
45. Murawski N, Pfreundschuh M, Zeynalova S, et al. Optimization of rituximab for the treatment of DLBCL (I): dose-dense rituximab in the DENSE-R-CHOP-14 trial of the DSHNHL. Ann Oncol. 2014;25(9):1800–1806. [PubMed: 24928834]
46. Pfreundschuh M, Poeschel V, Zeynalova S, et al. Optimization of rituximab for the treatment of diffuse large B-cell lymphoma (II): extended rituximab exposure time in the SMARTE-R-CHOP-14 trial of the German high-grade non-Hodgkin lymphoma study group. J Clin Oncol. 2014;32(36):4127–4133. [PubMed: 25403207]
47. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503–511. [PubMed: 10676951]
48. Liu Y, Barta SK. Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. Am J Hematol. 2019;94(5):604–616. [PubMed: 30859597]
49. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: definition and treatment. Cancer. 2018;124(24):4622–4632. [PubMed: 30252929]
50. Nowakowski GS, Czuczman MS. ABC, GCB, and double-hit diffuse large B-cell lymphoma: does subtype make a difference in therapy selection? Am Soc Clin Oncol Educ Book. 2015;35:e449–e457.
51. Phuoc V, Sandoval-Sus J, Chavez JC. Drug therapy for double-hit lymphoma. Drugs Context. 2019;8:1–13.

52. Morschhauser F, Feugier P, Flinn IW, et al. A phase 2 study of venetoclax plus R-CHOP as first-line treatment for patients with diffuse large B-cell lymphoma. Blood. 2021;137(5):600–609. [PubMed: 33538797]

53. Dunleavy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol. 2018;5(12):e609–e617. [PubMed: 30501868]

54. Dunleavy K, Pittaluga S, Maeda LS, et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med. 2013;368(15):1408–1416. [PubMed: 23574119]

55. Sparano JA, Lee JY, Kaplan LD, et al. ; AIDS Malignancy Consortium. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood. 2010;115(15):3008–3016. [PubMed: 20023215]

56. Wilson WH, Pittaluga S, Nicolae A, et al. A prospective study of mediastinal gray-zone lymphoma. Blood. 2014;124(10):1563–1569. [PubMed: 25024303]

57. Wilson WH, Dunleavy K, Pittaluga S, et al. Phase II study of dose-adjusted EPOCH and rituximab in untreated diffuse large B-cell lymphoma with analysis of germinal center and post-germinal center biomarkers. J Clin Oncol. 2008;26(16):2717–2724. [PubMed: 18378569]

58. Purroy N, Bergua J, Gallur L, et al. Long-term follow-up of dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor prognosis large B-cell lymphoma. A phase II study conducted by the Spanish PETHEMA Group. Br J Haematol. 2015;169(2):188–198. [PubMed: 25521006]

59. Bartlett NL, Wilson WH, Jung S-H, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III Intergroup Trial Alliance/CALGB 50303. J Clin Oncol. 2019;37(21):1790–1799. [PubMed: 30939090]

60. Wilson WH, Jung S-H, Porcu P, et al. ; Cancer Leukemia Group B. A Cancer and Leukemia Group B multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma with analysis of outcome by molecular subtype. Haematologica. 2012;97(5):758–765. [PubMed: 22133772]

61. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014;124(15):2354–2361. [PubMed: 25161267]

62. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. Blood. 2013;121(20):4021–4031. [PubMed: 23449635]

63. Dunleavy K, Fanale M, LaCasce A, et al. Preliminary report of a multicenter prospective phase II study of DA-EPOCH-R in MYC-rearranged aggressive B-cell lymphoma [ASH abstract 395]. Blood. 2014;124(21)(suppl).

64. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated immunochemotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. Br J Haematol. 2015;170(4):504–514. [PubMed: 25907897]

65. Magnusson T, Narkhede M, Mehta A, Goyal G. no difference in overall survival between R-CHOP and R-EPOCH among patients with advanced stage MYC-rearranged, double hit, or triple hit diffuse large B-cell lymphoma. Paper presented at: EHA 2021 Virtual Congress; June 9–17, 2021. Abstract S224.

66. Giulino-Roth L How I treat primary mediastinal B-cell lymphoma. Blood. 2018;132(8):782–790. [PubMed: 29976557]

67. Rieger M, Österborg A, Pettengell R, et al. Primary mediastinal B-cell lymphoma treated with CHOP-like chemotherapy with or without rituximab: results of the Mabthera International Trial Group study. Ann Oncol. 2011;22(3):664–670. [PubMed: 20724576]

68. Savage KJ, Al-Rajhi N, Voss N, et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. Ann Oncol. 2006;17(1):123–130. [PubMed: 16236753]

69. Shah NN, Szabo A, Huntington SF, et al. R-CHOP *versus* dose-adjusted R-EPOCH in frontline management of primary mediastinal B-cell lymphoma: a multi-centre analysis. Br J Haematol. 2018;180(4):534–544. [PubMed: 29265182]

70. Chan EHL, Koh LP, Lee J, et al. Real world experience of R-CHOP with or without consolidative radiotherapy vs DA-EPOCH-R in the first-line treatment of primary mediastinal B-cell lymphoma. Cancer Med. 2019;8(10):4626–4632. [PubMed: 31264808]

71. Dunleavy K, Wilson WH. How I treat HIV-associated lymphoma. Blood. 2012;119(14):3245–3255. [PubMed: 22337719]

72. Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood. 2005;106(5):1538–1543. [PubMed: 15914552]

73. Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood. 2003;101(12):4653–4659. [PubMed: 12609827]

74. Barta SK, Xue X, Wang D, et al. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. Blood. 2013;122(19):3251–3262. [PubMed: 24014242]

75. Pilichowska M, Pittaluga S, Ferry JA, et al. Clinicopathologic consensus study of gray zone lymphoma with features intermediate between DLBCL and classical HL. Blood Adv. 2017;1(26):2600–2609. [PubMed: 29296913]

76. Kritharis A, Pilichowska M, Evens AM. How I manage patients with grey zone lymphoma. Br J Haematol. 2016;174(3):345–350. [PubMed: 27301470]

77. Evens AM, Kanakry JA, Sehn LH, et al. Gray zone lymphoma with features intermediate between classical Hodgkin lymphoma and diffuse large B-cell lymphoma: characteristics, outcomes, and prognostication among a large multicenter cohort. Am J Hematol. 2015;90(9):778–783. [PubMed: 26044261]

78. Sarkozy C, Molina T, Ghesquières H, et al. Mediastinal gray zone lymphoma: clinico-pathological characteristics and outcomes of 99 patients from the Lymphoma Study Association. Haematologica. 2017;102(1):150–159. [PubMed: 27758822]

79. García-Suárez J, Bañas H, Arribas I, De Miguel D, Pascual T, Burgaleta C. Dose-adjusted EPOCH plus rituximab is an effective regimen in patients with poor-prognostic untreated diffuse large B-cell lymphoma: results from a prospective observational study. Br J Haematol. 2007;136(2):276–285. [PubMed: 17233819]

80. Ruppert AS, Dixon JG, Salles G, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. Blood. 2020;135(23):2041–2048. [PubMed: 32232482]

81. Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma. Blood. 2009;113(24):6069–6076. [PubMed: 19380866]

82. Hardefeldt P, Moore J, Milliken S, et al. Dose adjusted R-EPOCH does not improve outcomes in high grade B cell lymphoma with double expressor status or gain of MYC/BCL2 [ASH abstract 5336]. Blood. 2019;134(1)(suppl).

83. Dodero A, Guidetti A, Tucci A, et al. Dose-adjusted EPOCH plus rituximab improves the clinical outcome of young patients affected by double expressor diffuse large B-cell lymphoma. Leukemia. 2019;33(4):1047–1051. [PubMed: 30631117]

84. Al-Sawaf O, Robrecht S, Bahlo J, et al. Richter transformation in chronic lymphocytic leukemia (CLL)-a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials. Leukemia. 2021;35(1):169–176. [PubMed: 32203141]

85. Rogers KA, Huang Y, Ruppert AS, et al. A single-institution retrospective cohort study of first-line R-EPOCH chemoimmunotherapy for Richter syndrome demonstrating complex chronic lymphocytic leukaemia karyotype as an adverse prognostic factor. Br J Haematol. 2018;180(2):259–266. [PubMed: 29193006]

86. Davids MS, Rogers KA, Tyekucheva S, et al. A multicenter phase II study of venetoclax plus dose-adjusted R-EPOCH (VR-EPOCH) for Richter's syndrome [ASCO abstract 8004]. J Clin Oncol. 2020;38(15)(suppl).
87. Cheah CY, Wirth A, Seymour JF. Primary testicular lymphoma. Blood. 2014;123(4):486–493. [PubMed: 24282217]
88. Ho JC, Dabaja BS, Milgrom SA, et al. Radiation therapy improves survival in patients with testicular diffuse large B-cell lymphoma. Leuk Lymphoma. 2017;58(12):2833–2844. [PubMed: 28482717]
89. Vitolo U, Chiappella A, Ferreri AJM, et al. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. J Clin Oncol. 2011;29(20):2766–2772. [PubMed: 21646602]
90. Ahmad SS, Idris SF, Follows GA, Williams MV. Primary testicular lymphoma. Clin Oncol (R Coll Radiol). 2012;24(5):358–365. [PubMed: 22424983]
91. Dholaria B, Vanegas YAM, Diehl N, et al. Cost analysis of R-CHOP versus dose-adjusted R-EPOCH in treatment of diffuse large B-cell lymphoma with high-risk features. Clin Hematol Int. 2020;2(3):117–124. [PubMed: 34595452]
92. Maurer MJ, Ghesquières H, Link BK, et al. Diagnosis-to-treatment interval is an important clinical factor in newly diagnosed diffuse large B-cell lymphoma and has implication for bias in clinical trials. J Clin Oncol. 2018;36(16):1603–1610. [PubMed: 29672223]
93. Loh KP, Baran A, Lee CY, et al. Patients with diffuse large B-cell lymphoma requiring urgent treatment: its implication on trial design and interpretation. Leuk Lymphoma. 2019;60(14):3569–3572. [PubMed: 31282781]
94. Wright GW, Huang DW, Phelan JD, et al. A probabilistic classification tool for genetic subtypes of diffuse large B cell lymphoma with therapeutic implications. Cancer Cell. 2020;37(4):551–568.e14. [PubMed: 32289277]
95. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med. 2018;24(5):679–690. [PubMed: 29713087]
96. Reddy A, Zhang J, Davis NS, et al. Genetic and functional drivers of diffuse large B cell lymphoma. Cell. 2017;171(2):481–494.e15. [PubMed: 28985567]
97. Dodero A, Guidetti A, Marino F, et al. Dose-adjusted EPOCH and rituximab (DA-EPOCH-R) treatment in dual expressor diffuse large B-cell and double/triple hit lymphomas: TP53 mutations influence on clinical outcome [ASH abstract 4116]. Blood. 2019;134(1)(suppl).
98. Godfrey JK, Nabhan C, Karrison T, et al. Phase 1 study of lenalidomide plus dose-adjusted EPOCH-R in patients with aggressive B-cell lymphomas with deregulated MYC and BCL2. Cancer. 2019;125(11):1830–1836. [PubMed: 30707764]
99. Rutherford SC, Abramson JS, Bartlett NL, et al. Phase I study of the Bcl-2 inhibitor venetoclax with DA-EPOCH-R as initial therapy for aggressive B-cell lymphomas [ASCO abstract 8003]. J Clin Oncol. 2020;38(15)(suppl).
100. Clinicaltrials.gov. Acalabrutinib with DA-EPOCH-R or R-CHOP for people with untreated diffuse large B-cell lymphoma. https://clinicaltrials.gov/ct2/show/NCT04002947. Updated September 5, 2021. Accessed September 7, 2021.

Table 1.

Selected Phase 3 Randomized Controlled Trials to Improve Upon R-CHOP-21

Clinical Trial	Comparison Groups	Patient Population	Outcomes	Conclusions
Studies of R-CHOP-21 Intensification				
Habermann, 2006[22]	Maintenance rituximab vs observation after R-CHOP-21 or CHOP-21	632 patients aged 60 y or older with untreated DLBCL	2-y FFS rate was higher with maintenance rituximab after CHOP (74% vs 45% with observation alone), but not with maintenance rituximab after R-CHOP (79% vs 77% with observation alone).	**Negative:** No benefit was found for maintenance rituximab after R-CHOP.
Pfreundschuh, 2008[33] (RICOVER-60)	6 or 8 cycles of CHOP-14 or R-CHOP-14	1222 patients aged 61–80 y with untreated DLBCL	3-y EFS was 47% after 6 cycles of CHOP-14, 53% after 8 cycles of CHOP-14, 67% after 6 cycles of R-CHOP-14, and 63% after 8 cycles of R-CHOP-14.	**Positive:** 6 cycles of R-CHOP-14 significantly improved EFS, PFS, and OS vs 6 cycles of CHOP-14, although no increase in OS was found for 8 cycles of R-CHOP-14 or CHOP-14 compared with 6 cycles.
Récher, 2011[30] (LNH03-2B)	R-ACVBP vs R-CHOP-21	380 patients aged 18–59 y with untreated DLBCL and age-adjusted IPI 1	3-y OS was 92% in the R-ACVBP group and 84% in the R-CHOP group.	**Positive:** Compared with standard R-CHOP, R-ACVBP significantly improved EFS, PFS, and OS.
Delarue, 2013[34] (LNH03-6B)	R-CHOP-14 vs R-CHOP-21	602 patients aged 60–80 y with untreated DLBCL and age-adjusted IPI 1	3-y EFS was 56% in the R-CHOP-14 group and 60% in the R-CHOP-21 group.	**Negative:** R-CHOP-14 did not improve efficacy compared with R-CHOP-21.
Cunningham, 2013[35]	R-CHOP-14 vs R-CHOP-21	1080 patients aged >18 y with untreated DLBCL	2-y OS was 83% in the R-CHOP-14 group and 81% in the R-CHOP-21 group.	**Negative:** R-CHOP-14 was not superior to R-CHOP-21.
Chiappella, 2017[36] (DLCL04)	R-CHOP-14 vs R-MegaCHOP-14 with or without consolidative transplantation	399 patients aged 18–65 y with untreated DLBCL and age-adjusted IPI 2–3	5-y OS was 78% in the consolidative transplant group and 77% in the non-transplant group.	**Negative:** R-MegaCHOP plus consolidative transplant did not improve OS.
Vitolo, 2017[37] (GOYA)	G-CHOP-21 vs R-CHOP-21	1418 patients aged >18 y with untreated advanced-stage DLBCL and IPI ≥2, IPI 1 if age ≤60 y, or IPI 0 and bulky disease	3-y PFS was 70% in the G-CHOP group and 67% in the R-CHOP group.	**Negative:** G-CHOP did not improve PFS compared with R-CHOP.
Lugtenburg, 2020[38] (HOVON-84)	R-CHOP-14 vs RR-CHOP-14 (R-CHOP-14 with extra rituximab on day 8 of the first 4 cycles)	574 patients aged 18–80 y with untreated stage II-IV DLBCL and age-adjusted IPI 1–3 for ages 18–65 y and age-adjusted IPI 0–3 for ages 66–80 y	3-y OS was 81% in the R-CHOP-14 group and 76% in the RR-CHOP-14 group.	**Negative:** RR-CHOP-14 did not improve CR rate, PFS, or OS compared with R-CHOP-14.
Ohmachi, 2021[39] (JCOG0601)	R-CHOP-21 with 8 doses of rituximab once every 3 wk vs RW-CHOP-21 (CHOP-21 with 8 doses of weekly rituximab)	421 patients aged 20–79 y with untreated DLBCL	3-y OS was 89% in the R-CHOP-21 group and 90% in the RW-CHOP-21 group.	**Negative:** RW-CHOP-21 did not improve PFS compared with R-CHOP-21.
XR-CHOP Studies				
Seymour, 2014[40] (MAIN)	Bevacizumab + R-CHOP (RA-CHOP) vs R-CHOP	787 patients aged > 18 y with untreated DLBCL	Median PFS was 40 mo in the RA-CHOP group and 43 mo in the R-CHOP group.	**Negative:** The trial was stopped early because of increased cardiotoxicity of RA-CHOP without prolongation of PFS.

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Clinical Trial	Comparison Groups	Patient Population	Outcomes	Conclusions
Thieblemont, 2017[41] (REMARC)	Maintenance lenalidomide or placebo following first-line treatment with R-CHOP **Cell of origin assessment**	650 patients aged 60–80 y with untreated stage II-IV DLBCL and age-adjusted IPI ≥ 1 who achieved a PR or CR after first-line R-CHOP	2-y PFS was 80% in the lenalidomide maintenance group and 75% in the placebo maintenance group.	**Positive:** Median PFS was significantly longer with maintenance lenalidomide than with placebo, although without a significant difference in OS. Median PFS was significantly longer with lenalidomide than with placebo for the GCB cell of origin group, although not for the non-GCB cell of origin group.
Davies, 2019[42] (REMoDL-B)	Bortezomib + R-CHOP-21 (RB-CHOP) vs R-CHOP-21 **Cell of origin assessment**	918 patients aged > 18 y with untreated DLBCL	30-mo PFS was 70% in the R-CHOP-21 group and 74% in the RB-CHOP-21 group.	**Negative:** RB-CHOP-21 did not improve PFS compared with R-CHOP-21. Further, bortezomib did not significantly affect PFS in either the ABC or GCB cell of origin group.
Younes, 2019[43] (PHOENIX)	Ibrutinib + R-CHOP-21 vs R-CHOP-21 **Cell of origin assessment**	838 patients aged > 18 y with untreated **non-GC–type** stage II-IV DLBCL and IPI ≥1	3-y EFS was 70% in the ibrutinib + R-CHOP-21 group and 67% in the R-CHOP-21 group	**Negative:** Ibrutinib + R-CHOP-21 did not improve EFS, PFS, or OS compared with R-CHOP-21. Further, the addition of ibrutinib did not improve EFS in the ABC cell of origin group.
Nowakowski, 2021[44] (ROBUST)	Lenalidomide + R-CHOP-21 (R2-CHOP) vs R-CHOP-21 **Cell of origin assessment**	570 patients aged > 18 y with untreated **ABC-type** stage II-IV DLBCL and IPI ≥2	2-y PFS was 67% in the R2-CHOP-21 group and 64% in the R-CHOP-21 group.	**Negative:** R2-CHOP-21 did not improve PFS compared with R-CHOP-21.

ABC, activated B-cell; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; FFS, failure-free survival; GCB, germinal center B-cell; G-CHOP, obinutuzumab plus CHOP; IPI, International Prognostic Index; mo, months; OS, overall survival; PFS, progression-free survival; PR, partial response; R-ACVBP, rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone; R-CHOP, rituximab plus CHOP; R-MegaCHOP, rituximab, cyclophosphamide, doxorubicin, and vincristine on day 1, and prednisone on days 1–5; R2-CHOP, lenalidomide and rituximab plus CHOP; RA-CHOP, bevacizumab and rituximab plus CHOP; RB-CHOP, bortezomib and rituximab plus CHOP; RR-CHOP, R-CHOP with extra rituximab; RW-CHOP, CHOP with weekly rituximab; wk, weeks; XR-CHOP, addition of a new therapeutic (“X”) to the R-CHOP backbone; y, year(s).

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Table 2.

R-CHOP vs DA-R-EPOCH for Various Subtypes of DLBCL

DLBCL Subtype	Recommended Regimens (in Preferred Order)	Evidence
Clinical and Biological Scenarios in Which DA-R-EPOCH Is Preferred		
High-grade B-cell lymphoma with DHL/THL	DA-R-EPOCH (only phase 2 data) or R-CHOP	Phase 2 data demonstrating high 5-y OS rates with DA-R-EPOCH vs historical rates with R-CHOP.
PMBL	DA-R-EPOCH (only phase 2 data) or R-CHOP + consolidative radiation	Phase 2 data demonstrating higher 5-y OS rates with DA-R-EPOCH vs historical rates with R-CHOP, and toxicities from consolidative radiation may potentially be avoided.
HIV-associated DLBCL	DA-R-EPOCH (only phase 2 data) or R-CHOP	Phase 2 data demonstrating higher 2-y OS rates with DA-R-EPOCH vs historical rates with R-CHOP.
GZL	DA-R-EPOCH (only phase 2 data) or R-CHOP	Phase 2 data demonstrating higher 3-y OS rates vs historical rates with R-CHOP.
Clinical and Biological Scenarios in Which DA-R-EPOCH vs R-CHOP Is Controversial		
High-risk IPI scores (IPI 3–5)	R-CHOP	Phase 3 intergroup trial showed no difference in OS on the basis of IPI risk group.
GCB type	R-CHOP	R-CHOP is the therapeutic standard for GCB DLBCL, which is the best prognostic subtype.
ABC type	R-CHOP	No high-quality data are available comparing R-CHOP vs DA-R-EPOCH.
DEL	R-CHOP	Phase 3 intergroup trial showed no difference in OS on the basis of DEL phenotype, although the study was likely underpowered for this post hoc analysis.
Richter syndrome	R-CHOP	Clinical trials are paramount for this very poor prognostic subtype. DA-R-EPOCH has significant rates of toxicity.
Testicular DLBCL	R-CHOP	No data are available comparing R-CHOP vs DA-R-EPOCH.

ABC, activated B-cell; DA-R-EPOCH, dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; DEL, double-expressor lymphoma; DHL, double-hit lymphoma; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; GZL, gray zone lymphoma; IPI, International Prognostic Index; OS, overall survival; PMBL, primary mediastinal B-cell lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; THL, triple-hit lymphoma; y, year(s).