Review

Clinical Efficacy and Safety in Relapsed/Refractory Diffuse Large B-Cell Lymphoma: A Systematic Literature Review

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Abstract

This systematic literature review was designed to assess information on the clinical efficacy and safety of interventions used in the treatment of refractory or relapsed diffuse large B-cell lymphoma (R/R DLBCL) and to perform a meta-analysis if possible. We searched databases (PubMed, EMBASE, and Cochrane Library for articles from 1997 to August 2, 2012 reported in English), conference abstracts, bibliographic reference lists, and the ClinicalTrials.gov database for phase II to IV studies with results. Studies had to report on patients with R/R DLBCL who were not eligible to receive high-dose therapy (HDT) with stem cell transplantation (SCT) (autologous or allogeneic). Mixed-type non-Hodgkin lymphoma (NHL) studies were required to report R/R DLBCL outcomes separately. We identified 55 studies that presented outcomes data separately for patients with R/R DLBCL. Of 7 comparative studies, only 4 were randomized controlled trials (RCTs). In the 2 RCTs with a common regimen, the patient populations differed too greatly to perform a valid meta-analysis. The 48 single-arm studies identified were typically small ($n < 50$ in most), with 31% reporting median progression-free survival (PFS) or overall survival (OS) specifically for the R/R DLBCL population. In these studies, median OS ranged from 4 to 13 months. The small number of RCTs in R/R DLBCL precludes identifying optimal treatments. Small sample size, infrequent reporting of OS and PFS separated by histologic type, and limited information on patient characteristics also hinder comparison of results. Randomized studies are needed to demonstrate which current therapies have advantages for improving survival and other important clinical outcomes in patients with R/R DLBCL.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Chemotherapy, Diffuse large B-cell lymphoma, Refractory, Relapsed

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most commonly occurring type of non-Hodgkin lymphoma (NHL), accounting for 30% to 40% of newly diagnosed NHL cases in Western countries.[1-3] The incidence of DLBCL increases markedly with age (overall, the annual incidence in the United States is estimated at 6.9 per 100,000, but it is 32.3 per 100,000 among individuals aged 65 years or older),[4] and the disease occurs more commonly among men (8.3 per 100,000)[5] than women (5.7 per 100,000).[6]

DLBCL is an aggressive lymphoma, and although current treatments result in long-term, disease-free survival in a substantial proportion of patients, overall only 30% to 50% of patients survive 5 years or more.[7] Most relapses of DLBCL occur early, but some may occur even after 5 years of remission.[8]

Rituximab, a chimeric anti-CD20 antibody, has significantly improved the response rate to first-line therapy for both young[9] and elderly patients,[10] and two thirds of patients may be cured with first-line combination chemotherapy (typically R-CHOP [rituximab plus cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine [Oncovin], and prednisone).[11] However, if treatment fails, particularly if treatment fails early, survival is usually measured in months.[12]

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Submitted: Dec 20, 2013; Revised: Feb 20, 2014; Accepted: Feb 24, 2014

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2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2014.02.012

Patients younger than 65 years who receive rituximab as part of first-line therapy have worse clinical outcomes (response rates, event-free survival, and overall survival [OS]) after relapse.[13] Older patients also show a trend toward lower survival when they received rituximab in first-line therapy.[12] Only high-dose therapy (HDT) (chemo-immunotherapy) followed by autologous stem cell transplantation (ASCT) offers the potential for long-term, disease-free survival for patients with chemosensitive disease at relapse.[11] Approximately half of patients with relapsed/refractory (R/R) disease are not eligible for HDT-ASCT because of age (typically older than 70-75 years), comorbidities, or lack of adequate social support to help with the care needed after transplantation.[11] Moreover, of patients who undergo HDT-ASCT, many will subsequently experience relapse.[13] For patients ineligible or unwilling to undergo HDT-ASCT or those whose disease relapses after HDT-ASCT, responses to recommended therapies are generally of short duration, and participation in a clinical trial of novel agents is often the preferred treatment option.[14]

Therapies in development should be compared with regimens already studied to establish their relative efficacy and safety for treating patients with R/R DLBCL after or instead of HDT-ASCT. In addition, appropriate design of clinical trials for new agents should be informed by existing studies in this patient population and setting.[15-17] To facilitate clinical trial design and interpretation of study results, it is recommended that 1 or more systematic literature reviews be identified that are current and relevant to the proposed research study.[16,17] To our knowledge, there is no current systematic literature review available that is focused on patients with DLBCL (as opposed to mixed populations with NHL), R/R disease (as opposed to initial therapy), and chemotherapy (including radioimmunotherapy and monoclonal antibody therapy) for patients who are ineligible for stem cell transplantation (SCT).[11]

This review was designed to systematically collect and review information on the clinical efficacy and safety of current non-ASCT treatments for R/R DLBCL and to perform a meta-analysis if possible. Because we anticipated a paucity of randomized controlled trials (RCTs), we also planned to determine the types of regimens being evaluated in single-arm studies and their individual efficacy.

Methods

Literature Search and Data Extraction

We systematically searched electronic databases (PubMed, EMBASE, and Cochrane Library) for studies assessing the efficacy and safety of treatments for R/R NHL published from 1997 to August 2, 2012 in English. In addition to the literature databases, we searched conference abstracts, bibliographic reference lists of included articles and recent reviews, and the ClinicalTrials.gov database for phase II, III, or IV studies with results. To identify recent studies that might not be published at the time of our database search, conference abstracts were searched from the 2011 and 2012 meetings of the American Society of Clinical Oncology and the European Hematology Association, and the 2010 and 2011 meetings of the American Society of Hematology, and the European Society for Medical Oncology.

The search for studies of DLBCL was part of a larger systematic literature search that also reviewed indolent lymphoma and mantle cell lymphoma. (Literature review results for indolent lymphoma and mantle cell lymphoma will be reported elsewhere.)

To identify studies on the disease types of interest, synonyms for NHL and the individual disease types of interest were used (Supplemental Table A-1). Search terms included medical subject headings and disease terms limited to the title/abstract. The search was restricted using medical subject headings and title/abstract terms for interventions, particularly pharmacotherapy. The search was also restricted to clinical studies by using the terms associated with clinical studies.

Assessment of each study for inclusion or exclusion was performed independently by 2 researchers in 2 steps. At step 1, titles and abstracts of all identified articles were screened. The full text of all articles determined to be eligible at step 1 was reviewed at step 2 to ensure that the articles met the inclusion criteria. At step 2, included articles were tracked by disease type of interest. All disagreements between the researchers were resolved by consensus, with input from an experienced senior researcher if necessary. Included studies were randomized or nonrandomized clinical studies evaluating chemotherapy in patients aged $\geq$ 18 years with R/R NHL (step 1 screening) reporting separate outcomes for patients with R/R DLBCL, mantle cell lymphoma, or indolent lymphoma (step 2 screening). Studies using the International Working Formulation for lymphoma classification were excluded because this system was based solely on histologic type[18]; was not reproducible; did not allow for distinction of lymphomas originating from T cells, B cells, or natural killer cells; and did not include many of the newly identified types of lymphoma. For the review of DLBCL, studies had to report outcomes on R/R DLBCL after at least 1 standard treatment in patients who were not eligible to receive HDT or SCT (autologous or allogeneic). Studies were included if patients underwent ASCT, but the outcomes (response rates) were reported after chemotherapy and before ASCT.

For studies included at step 2 screening, full data extraction was performed on the comparative studies (nonrandomized but controlled trials with 2 or more treatment arms and RCTs). An abbreviated extraction was performed for the single-arm studies. Extracted data included study details (eg, design, period of study); treatments administered and line of therapy; inclusion and exclusion criteria; end points reported; patient characteristics (mean age, percentage male, performance status, International Prognostic Index); number of previous regimens; duration of follow-up; objective, complete, and partial response rates; duration of response; median progression-free survival (PFS); median OS; and safety outcomes, particularly hematologic toxicities.

Quality assessment for RCTs was performed based on guidance in the National Institute for Health and Care Excellence "Single Technology Appraisal (STA) Specification for Manufacturer/Sponsor Submission of Evidence 2009"[19] and adapted from the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care.[20]

Data Synthesis

The feasibility of meta-analysis was evaluated based on the articles identified through this search. Because meta-analysis with RCTs is considered the gold standard, the decision was made to focus on the RCTs. The intention was to conduct a direct meta-analysis if possible or an indirect meta-analysis for agents not evaluated directly against one another.

Results

Study Identification and Meta-Analysis Feasibility

A total of 3216 records were obtained through electronic database searches, and 14 records were obtained from cancer organization meeting abstracts (American Society of Clinical Oncology, American Society of Hematology, European Hematology Association, and European Society for Medical Oncology), bibliographic listings, and ClinicalTrials.gov (Fig. 1). In total, 58 sources represented 55 studies with outcomes for patients with R/R DLBCL. Comparative studies were defined as those with more than 1 treatment group, with or without randomization. Of the 55 R/R DLBCL studies, 7 were comparative, but only 4 of the studies (in 5 records) were RCTs; 48 were single-arm studies. Meta-analysis was not feasible for these RCTs; only 2 of the RCTs[21,22] had a regimen in common (ESHAP [etoposide, methylprednisolone {solumedrol}, cytarabine {Ara-C}, and cisplatin {platinum}]), but the patient populations in these 2 trials differed by age and performance status. In the study by Aribi et al,[21] patients were aged 60 to 70 years, and Eastern Cooperative Oncology Group (ECOG) performance status was 0, 1, or 2. However, in the study by Aviles et al,[22] patients were aged 32 to 63 years, and ECOG performance status was 2 or higher. Therefore, indirect comparison between GDP (gemcitabine, dexamethasone, cisplatin [platinum]) and R-ESHAP (rituximab plus ESHAP) based on these 2 trials was inadvisable because of the differences in patient populations. Because meta-analysis was not feasible for the R/R DLBCL studies, results of this systematic review are summarized qualitatively only.

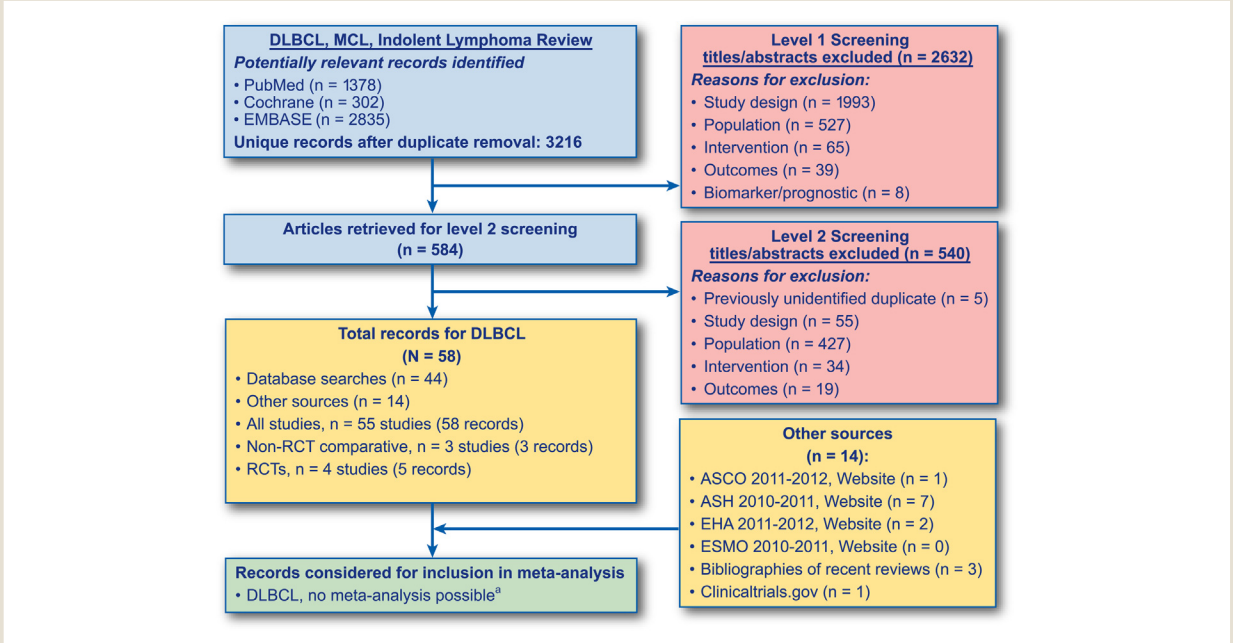
Study Characteristics

Supplemental Table A-2 presents the quality assessments of the 4 RCTs. The treatment groups in all 4 trials were similar at baseline. One of the studies reported being a single-blind study with no further explanation,[21] but given the nature of the disease and treatments, presumably the assessor was blinded. Two other studies gave no information regarding blinding.[13,22] The fourth study was reported in conference abstracts, and no details were given about blinding.[23,24] Information on dropout rates was presented in 2 of the RCTs[13,21] but not in the other 2 RCTs.[22-24]

Of the 7 comparative studies, 4 included fewer than 50 patients with R/R DLBCL,[23,25-27] and 3 included nearly 100 or more patients.[13,21,22] The number of patients with R/R DLBCL in single-arm studies was generally fewer than 50 patients (41 of 48 studies). Of the single-arm studies with 50 or fewer patients with DLBCL, 8 studies included fewer than 10 patients,[28-35] 11 included 10 to 20 patients,[36-46] 11 included 21 to 30 patients,[47-57] 7 included 31 to 40 patients,[58-65] and 4 included 41 to 50 patients.[66-69] Of the larger single-arm studies, the number of patients with R/R DLBCL was 51 to 81 in 5 studies,[10,70-74] 104 in 1 study,[75] and 108 in another study.[76]

Of the 48 regimens evaluated in the R/R DLBCL studies, few regimens were represented more than once. In the RCTs, only ESHAP was evaluated in more than 1 study,[21,22] but the populations differed considerably (as noted previously). In addition to ESHAP, regimens evaluated in more than 1 R/R DLBCL comparative or noncomparative study were rituximab plus bendamustine,[25,62,71] rituximab plus lenalidomide,[32,50] R-ESHAP,[22,58] R-ICE

Figure 1 Flow Diagram of Study Inclusion and Exclusion (PRISMA Diagram)



Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; DLBCL = diffuse large B-cell lymphoma; EHA = European Hematology Association; ESMO = European Society for Medical Oncology; MCL = mantle cell lymphoma; RCT = randomized controlled trial.
[a]Two of the 3 RCTs in patients with DLBCL had a regimen in common, but the patient populations in these 2 trials differed by age and performance status.

(rituximab plus ifosfamide, carboplatin, and etoposide),[13,26,60] paclitaxel,[31,59] and ^{90}Y–ibritumomab tiuxetan.[37,75]

Only 5 studies provided definitions for R/R disease (Table 1). The definitions varied, with a stricter definition of refractory in 2 studies (absence of a complete response in 2 studies)[13,56] than in 2 other studies (partial response[31] or less than a partial response[66]). Similarly, relapsed had a stricter definition in 1 study (disease progression after a complete response)[56] than in another study (disease progression after achieving at least a partial response).[31]

Efficacy Outcomes: R/R DLBCL Comparative Studies

Table 2 summarizes the efficacy outcomes of the comparative trials of patients with R/R DLBCL. The overall response rate (ORR) of active treatments in all patients treated ranged from 27% with high-dose obinutuzumab monotherapy[23,24] to 78% with R-ICE.[26] After second-line treatment, 23 patients with relapsed DLBCL had a 96% ORR with R-ICE, whereas 13 patients with refractory DLBCL had only a 46% ORR ($P < .01$).[26]

Only 1 of the comparative studies reported response duration,[23,24] which ranged from 6.3 months to 9.8 months in the 3 responders of 30 patients receiving low-dose obinutuzumab and from 3.1 months to 19.5 months in the 5 of 27 patients responding to high-dose obinutuzumab.

Median PFS was reported only for the study of low-dose (1.9 months) and high-dose obinutuzumab (2.7 months).[23,24] Other studies reported PFS at various specific time points (ie, 2-, 3-, or 5-year PFS (Table 2).[13,21,22,26] The proportion of patients with 3-year PFS was lower after ESHAP treatment (10.9%) in the study by Aribi et al[21] than the proportion with 5-year PFS (51%) in the study by Aviles et al,[22] despite that the latter study enrolled frail patients (ECOG performance status $\geq$ 2) and the ORRs were similar (Table 2). Most of the patients (54%; 211 of 388) in the study by Gisselbrecht et al[13] underwent ASCT, and the study did not report 3-year PFS separately for ASCT-eligible and ASCT-ineligible patients. The proportion of patients without progression at 3 years was similar in the R-ICE (31%) and R-DHAP (rituximab plus dexamethasone, cytarabine [Ara-C], and cisplatin) (42%) groups (Table 2).

Median OS with MEP (mitoxantrone, etoposide, and prednisone) or C-MEP (carboplatin plus MEP) was short (4-7 months).[27] The other comparative studies reported the proportion of patients alive at the aforementioned specific time points (Table 2).[21,22,26] In the RCTs, OS outcomes reflected PFS outcomes. The proportion of patients with 3-year OS after ESHAP treatment (11.8%) was lower in the study by Aribi et al than the proportion with 5-year OS (31%) in the study of frail patients by Aviles et al, and the proportion of patients still alive at 3 years was similar in the R-ICE (47%) and R-DHAP (51%) groups for all patients treated, including those who underwent ASCT.[13,21,22] Gisselbrecht et al[13] reported 3-year OS for all patients, including most patients who underwent ASCT.

Of the comparative studies in this review, only the study by Gisselbrecht et al[13] had populations with and without previous rituximab treatment, so only this study could assess the effect of rituximab treatment history. Response rates and survival were higher for patients who had not received previous rituximab compared with those who had (complete and unconfirmed complete responses and partial responses, 83% vs. 51%; $P < .001$ for rituximab naive vs. previous rituximab groups; 3-year event-free survival, 47% vs. 21%; $P < .001$; 3-year OS, 66% vs. 40%; $P < .01$).[13]

Table 1 Definitions of Relapsed or Refractory Disease in the Identified Studies of Diffuse Large B-Cell Lymphoma

Reference	Definition of Relapsed or Refractory Disease
Cheson et al, 2012[66]	Refractory to the last treatment was defined as achieving less than a partial response or at least a partial response that lasted <6 months before disease progression
Gisselbrecht et al, 2010[13]	Relapse: not defined Refractory: did not achieve a complete response with a standard anthracycline-based regimen (CHOP)
Gyan et al, 2010[68]	First relapse was defined as having obtained at least a partial response of >50% to an anthracycline-based front-line regimen
Jerkeman et al, 2004[56]	Relapse was defined as disease progression, verified by biopsy, after an initial complete remission Primary progressive disease was defined as progression in a patient without attaining complete remission
Kahl et al, 2005[31]	Relapse was defined as disease progression after achieving at least a partial response to the most recent systemic therapy Refractory was defined as having had less than a partial response to the most recently administered systemic therapy

Abbreviation: CHOP = cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (Oncovin), and prednisone.

Efficacy Outcomes: R/R DLBCL Noncomparative Single-Arm Studies

In the single-arm studies, ORR ranged from 11% to 97% (Fig. 2). Although single-arm studies could not be compared directly, we graphed the ORRs to look for trends by radioimmunotherapy, combinations of more than 2 drugs not including rituximab, combinations of more than 2 drugs including rituximab, monotherapies, dual-agent regimens including rituximab, and dual-agent regimens not including rituximab. We also grouped the results by R/R DLBCL population size (> 50 patients, 16-50 patients, and < 16 patients). Within each sample size category, the monotherapies tended to consistently show lower ORRs than the other treatment groupings, except for 1 relatively high ORR with paclitaxel in a study with 6 patients[31] (Fig. 2). The study of paclitaxel monotherapy allowed premedication with dexamethasone (20 mg intravenously), which may have augmented the response to therapy, and a very small number of patients were treated.[31]

Across all size groupings, the range of ORRs for the regimens with rituximab added to a single agent was visually similar to the range of radioimmunotherapy regimens, although there were few studies with radioimmunotherapy.[30,37,75] In the midsized group (16-50 patients), the range of ORRs for regimens with rituximab added to a single agent was somewhat lower than the ranges for the combinations of more than 2 drugs with and without rituximab; this pattern is less clear in the studies with fewer than 16 patients (Fig. 2). Except for a high ORR with R-ESHAP[58] and a low ORR with DHAOx (dexamethasone, high-dose cytarabine [Ara-C], and oxaliplatin),[28] the ranges of regimens with more than 2 drugs were visually similar between the groups with and without rituximab

when looking across all the single-arm studies. However, this pattern is weaker among the midsized group (16-50 patients) because only 3 data points were available for the combinations of more than 2 drugs without rituximab.[46,52,67] There were only 2 dual-agent regimens without rituximab: gemcitabine plus vinorelbine[48] and oral vorinostat plus bortezomib.[54] The ORR with gemcitabine plus vinorelbine[48] was in the same range as the ORR with rituximab added to 1 drug, but the ORR with oral vorinostat plus bortezomib[54] was considerably lower.

In the largest study reporting median duration of response in patients with DLBCL, median response duration was 6.9 months (95% confidence interval [CI], 5.3-6.9) in 9 of 81 treated patients who responded to ofatumumab.[10,74] In 1 of 2 midsized studies, median response duration was 11.3 months (range, 1.8-18.5 months) for 7 of 37 treated patients who responded to tipifarnib.[64,65,67] In 1 of 2 small studies, median response duration was 6 months in 12 of 15 treated patients who responded to rituximab plus epratuzumab.[72] In the other small study, median response

Table 2 Comparative Studies Involving Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Efficacy Data

Reference	No. of Patients[a]	ORR (%)[b]	Duration of Response, mo	Median PFS	Median OS
RCTs					
Aribi et al, 2010[21]	96 with DLBCL: ESHAP, n = 48 GDP, n = 48	ESHAP, 55 GDP, 63 *P* = .01	NR	NR 3-year PFS, %[c] (95% CI): ESHAP, 10.9 (8.2-13.7) GDP, 20.5 (16.3-24) *P* = .0003	NR 3-year OS, %[d] (95% CI): ESHAP, 11.8 (8.9-14.6) GDP, 20.5 (16.5-24.5) *P* = .001
Aviles et al, 2010[22]	100 with DLBCL: ESHAP, n = 53 R-ESHAP, n = 47	ORR (95% CI) ESHAP, 62 (55-69) R-ESHAP, 60 (50-69)	NR	5-year PFS, %[e] (95% CI): ESHAP, 51 (43-60) R-ESHAP, 50 (42-58) *P* = .6 (NS)	5-year OS, %[f] (95% CI): ESHAP, 31 (24-38) R-ESHAP, 26 (21-39) *P* = .8 (NS)
Gisselbrecht et al, 2010[13]	388 with DLBCL: R-ICE, n = 197 R-DHAP, n = 191	R-ICE, 63.5%[g] R-DHAP, 62.8%[g]	NR	NR 3-year PFS, all patients[h] R-ICE, 31% R-DHAP, 42% *P* = .4	NR 3-year OS, all patients[h] R-ICE, 47% R-DHAP, 51% *P* = .4
Morschhauser et al, 2011[23] and Cartron et al, 2010[24]	40 Low-dose obinutuzumab, 10 with DLBCL High-dose obinutuzumab, 15 with DLBCL	Low-dose obinutuzumab, 30 High-dose obinutuzumab, 27	3 responders in low-dose group: 6.3, 8.6, 9.8 5 responders in high-dose group: 3.1, 3.1+, 5.8, 16.5+, 19.5	Low-dose, 1.9 mo (range, 0.3-15.7 mo) High-dose, 2.7 mo (range, 0.2-22.3 mo)	NR
Non-RCT Comparative					
Murohashi et al, 2002[27]	49 with DLBCL MEP, 22 (14 CHOP resistant) C-MEP, 27 (24 CHOP resistant)	All: MEP, 41 C-MEP, 48 *P* = .602 (NS) CHOP-resistant: MEP, 7 C-MEP, 42 *P* = .024	NR	NR	All MEP, 4 mo (95% CI, 3.2-4.8 mo) C-MEP, 7 mo (95% CI, 0.0-18.0 mo) *P* = .165 (NS) CHOP resistant OS higher for C-MEP versus MEP, but *P* = .088) (NS)
Ogura et al, 2011[25]	9 90-mg/m^2 dose bendamustine plus rituximab, 3 with DLBCL 120 mg/m^2 dose bendamustine plus rituximab, 2 with DLBCL	90 mg/m^2 bendamustine plus rituximab, 33[i] 120 mg/m^2 dose bendamustine plus rituximab,100	NR	NR	NR

Table 2 Continued

Reference	No. of Patients[a]	ORR (%)[b]	Duration of Response, mo	Median PFS	Median OS
Kewalramani et al, 2004[26]	R-ICE, 36 with DLBCL (37 for toxicity—1 patient misdiagnosed) ICE, historical control group, 147 with DLBCL	All patients: R-ICE, 78 Historical ICE, 71 $P = .53$ (NS) Relapsed: R-ICE, 96 Historical ICE, 79 $P = .07$ (NS) Refractory: R-ICE, 46 Historical ICE, 63 $P = .36$ (NS) sAAIPI L/L-I: R-ICE, 79 Historical ICE, 86 $P = .47$ (NS) sAAIPI H-I/H: R-ICE, 76 Historical ICE, 61 $P = .28$ (NS)	NR	2-year PFS after ASCT (95% CI): R-ICE (n = 23), 54% (38%-78%) Historical ICE, (n = 95), 43% (34%-55%) $P =$ NS	2-year OS after ASCT (95% CI): R-ICE (n = 23), 67% (50%-89%) Historical ICE, (n = 95), 56% (47%-67%) $P =$ NS

Abbreviations: ASCT = autologous stem cell transplantation; CHOP = cyclophosphamide, doxorubicin, vincristine (Oncovin), prednisone; CI = confidence interval; C -MEP = carboplatin, mitoxantrone, etoposide, prednisone; DLBCL = diffuse large B-cell lymphoma; ESHAP = etoposide, cisplatin, methylprednisolone (solumedrol), cytarabine (Ara-C); GDP = gemcitabine, cisplatin, dexamethasone; H-I/H = high-intermediate/high; ICE = ifosfamide, carboplatin, etoposide; L/L-I = low/low-intermediate; MEP = mitoxantrone, etoposide, prednisone; NR = not reported; NS = not significant; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; R-DHAP = rituximab plus dexamethasone, cytarabine [Ara-C], cisplatin; R-ESHAP = rituximab plus etoposide, cisplatin, methylprednisolone (solumedrol), cytarabine (Ara-C); R-ICE = rituximab plus ifosfamide, carboplatin, etoposide; sAAIPI = second-line age-adjusted International Prognostic Index.

[a]Number of patients with relapsed/refractory (R/R) DLBCL. For RCTs, the number of patients presented is the number randomized.

[b]Cheson criteria.[82]

[c]Progression-free survival was defined as survival without recurrence (no relapse or signs of progression after treatment).[21]

[d]The Aribi et al[21] article presents 2 sets of 3-year OS and PFS outcomes. The outcomes shown in the table of this report were taken from the text in the Results section of the article. The alternative outcomes were presented in Table 2 of the article but were not called "3-year" outcomes; however, these were the numbers summarized in the Discussion section as 3-year outcomes.

[e]PFS was defined as the time from study entry until disease progression.[22]

[f]Overall survival was defined as the time from start of treatment to death regardless of cause.[22]

[g]Overall response rates were determined after salvage chemotherapy and before ASCT.[13]

[h]Of the 398 patients in this study, 211 underwent ASCT; survival outcomes include patients who did and those who did not undergo ASCT.[13]

duration for 7 responders among 12 patients with DLBCL treated with ^{90}Y–ibritumomab tiuxetan was 49.8 months because of response durations of > 60 months in 2 patients.[37]

In 12 studies reporting separate rates for patients with R/R DLBCL, median PFS was approximately 1 to 10 months.[10,42,45,47,49,52,53,57,70-72,74,76] In these few studies, separation by study size did not elucidate a pattern among the different treatment groups (Fig. 3). Also, there was no discernible pattern between the most represented treatment groups: dual-agent regimens with rituximab and monotherapies (Fig. 3). However, median PFS was consistently low among the monotherapy studies (2-3 months) (Fig. 3). PFS was less than 4 months in 8 studies (Fig. 3).[10,42,45,47,49,53,70,74,76]

Reported median OS ranged from 4 to 13 months without patient stratifications (Table 3).[41,47,48,70] Patients without a complete response to GDP treatment had a median OS of 27.4 months, whereas the median was not reached for patients with a complete response.[73] OS was not reached in a study with a short duration of follow-up (median, 5.2 months).[38]

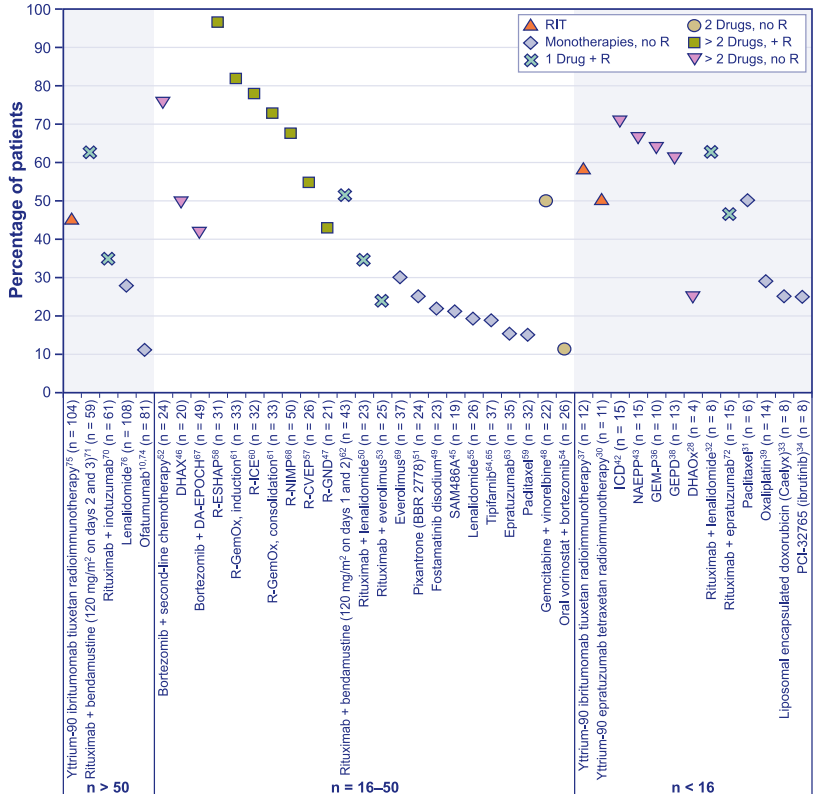
Of the noncomparative studies, only 1 study reported outcomes by rituximab history.[75] After ^{90}Y–ibritumomab tiuxetan radioimmunotherapy, the ORR for 76 rituximab-naive patients was 53% compared with 19% among 28 patients with a history of rituximab therapy. Another study did not present data but noted that similar proportions of responders and nonresponders to epratuzumab had received rituximab previously.[63] Survival rates were not reported for the R/R DLBCL populations in these 2 studies. Graphic analysis of the 22 studies that either reported the rituximab history of the patients with R/R DLBCL or were clearly conducted before rituximab availability showed no particular pattern regarding ORRs by rituximab history (Supplemental Fig. 1). However, the number of studies within each grouping shown in Figure 2, and then by rituximab history was small, and other confounding factors, such as duration of rituximab treatment, were not reported.

The following were considered by the investigators to be failed regimens, and the data on patients with R/R DLBCL from these single-arm phase II studies are not included in the earlier efficacy description: clofarabine (grade 3/4 adverse events in 5 of 6 patients and prolonged [> 28 days] myelosuppression in 4 of 6 patients),[29] sunitinib (no complete or partial responses in 15 patients),[40] oral vorinostat (1 complete and 1 partial response in 18 patients, and slow trial accrual),[44] YM155 (futility analysis on 25 evaluable patients showed that there was only an estimated 1.1% probability of achieving the protocol-specified minimum response rate after 50 evaluable patients [ie, 18%] and an estimated 0.2% probability of achieving the protocol-specified minimum response rate after 200 evaluable patients [26%]),[66] ICE (failed based on mobilization rate of peripheral blood stem cells),[56] and oblimersen plus rituximab (2 partial responses and no complete responses in 9 patients).[35]

Safety Outcomes: R/R DLBCL Comparative and Noncomparative Studies

In comparative studies in R/R DLBCL, the main grade 3/4 adverse events were hematologic (Fig. 4). In the study by

Figure 2 Objective Response Rates in Noncomparative Studies



The study of paclitaxel monotherapy allowed premedication with dexamethasone (20 mg intravenously), which may have augmented the response to therapy.[31] The responses were generally brief (median response duration of 3.2 months [range, 1.4-11.8 months]). The response durations were similarly brief in another study of paclitaxel monotherapy,[59] and the ORR was quite low (12.5%) for patients with DLBCL and for all the patients with NHL in the study. This latter study was not included in the figure because paclitaxel was considered a failed regimen by the investigators.
Abbreviations: DA-EPOCH = dose-adjusted infusional etoposide, vincristine, and doxorubicin, with cyclophosphamide and prednisone; DHAOx = dexamethasone, high-dose cytarabine (Ara-C), and oxaliplatin; DHAX = dexamethasone, cytarabine, and oxaliplatin; GEM-P = gemcitabine, cisplatin, and methylprednisolone (solumedrol); NAEPP = vinorelbine, epirubicin, and prednisone; R = rituximab; R-CVEP = rituximab, cyclophosphamide, vorinostat, etoposide, and prednisone; R-ESHAP = rituximab, etoposide, methylprednisolone (solumedrol), cytarabine (Ara-C), and cisplatin; R-GemOx = rituximab, gemcitabine, and oxaliplatin; R-GND = rituximab, gemcitabine, vinorelbine, and liposomal doxorubicin; R-ICE = rituximab, ifosfamide, carboplatin, and etoposide; RIT = radioimmunotherapy; R-NIMP = rituximab, vinorelbine, ifosfamide, mitoxantrone, and prednisone.

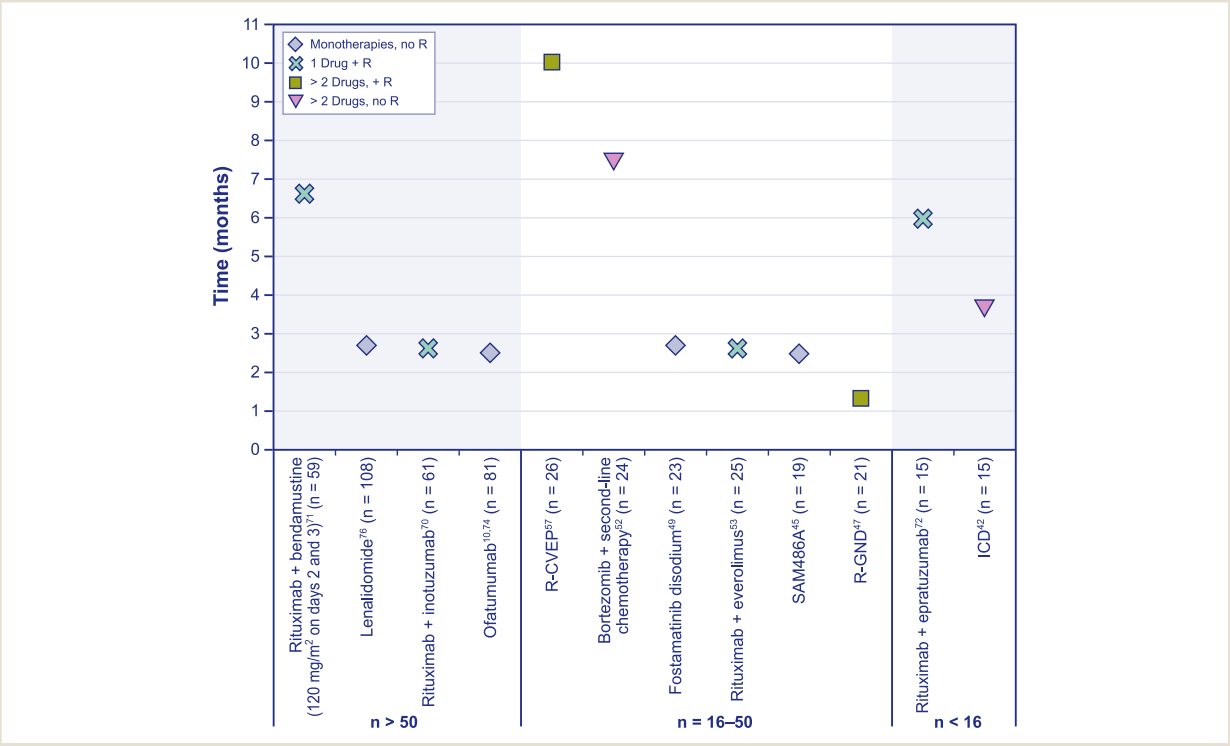
Gisselbrecht et al,[13] more patients treated with R-DHAP (57%) required platelet transfusions because of more severe hematologic adverse events than did patients treated with R-ICE (35%). The study by Aribi et al comparing ESHAP and GDP in elderly patients found a significantly lower rate of grade 3/4 leukopenia with GDP ($P = .0001$),[21] with the highest rate for grade 4 leukopenia (44% with ESHAP vs. 6.2% with GDP). However, the rates of grade 3/4 thrombocytopenia were significantly higher for patients receiving GDP (41% vs. 11.6% with ESHAP; $P = .001$).

Grade 3/4 infection-related pneumonia was common in the RCT comparing ESHAP (49% of cycles) with R-ESHAP (71% of cycles) in frail patients.[22] The most common serious adverse events in the RCT comparing R-ICE and R-DHAP were infections as a result of neutropenia (16% in both arms).[13] Grade 3/4 vomiting was common with ESHAP (31%) and GDP (29%) in the study by Aribi et al.[21]

Toxicity-related death occurred in 1 patient treated with R-ICE and in 3 patients treated with R-DHAP in the study by Gisselbrecht et al[13] and in 1 patient (4.5%) treated with MEP in the study by Murohashi et al.[27]

The main grade 3/4 adverse events reported in noncomparative studies were also hematologic (Fig. 5). Grade 3/4 thrombocytopenia occurred in 4% to 39%, leukopenia in 0% to 38%, anemia in 4% to 42%, febrile neutropenia in 4% to 32%, and neutropenia in 13% to 100% of patients. All the patients treated with alternating MiCMA (mitoxantrone, carboplatin, cytarabine, and methylprednisolone) and IGEV (ifosfamide, gemcitabine, and vinorelbine) regimens experienced grade 3/4 neutropenia.[41] In a study of ^{90}Y–ibritumomab tiuxetan radioimmunotherapy, severe infections led to hospitalization in 7% of patients, and nonprogression-related deaths occurred in 6 patients.[75] A study of ofatumumab found that 59% of patients experienced infusion-related events, but 96% of these were grade 1 or 2 in severity, and the rate of infusion reactions diminished during subsequent infusions.[10,74] In a study of bortezomib added to second-line chemotherapy, 7 deaths occurred among the 24 patients within the median 8 months of follow-up; 5 deaths were caused by disease progression, with 4 patients having central nervous system infiltrates, and 2 deaths resulted from severe infections. Although the efficacy was promising (1-year OS of 65%), central nervous system relapse and infections were relatively common.[52]

Figure 3 Median Progression-Free Survival in Noncomparative Studies



Abbreviations: ICD = irinotecan, cisplatin, and dexamethasone; R = rituximab; R-CVEP = rituximab, cyclophosphamide, vorinostat, etoposide, and prednisone; R-GND = rituximab, gemcitabine, vinorelbine, and liposomal doxorubicin.

Discussion

To our knowledge, this is the first systematic literature review to report selectively on patients with R/R DLBCL. A systematic review includes an extensive search for relevant data and ensures critical appraisal of the available evidence. For this literature review, we stipulated that studies included for analysis would have at least 1 efficacy or safety outcome, or both, presented separately for DLBCL when patients with other lymphoma types were included in the study. We identified a fairly large number of studies with this kind of evidence. However, most were single-arm studies; there were few comparative studies and even fewer RCTs (7 comparative studies including 4 RCTs). Although the intended goal of this literature review was to conduct a meta-analysis, there was a common treatment in only 2 of the RCTs, but the patient populations in these studies differed too greatly to enable a valid meta-analysis.

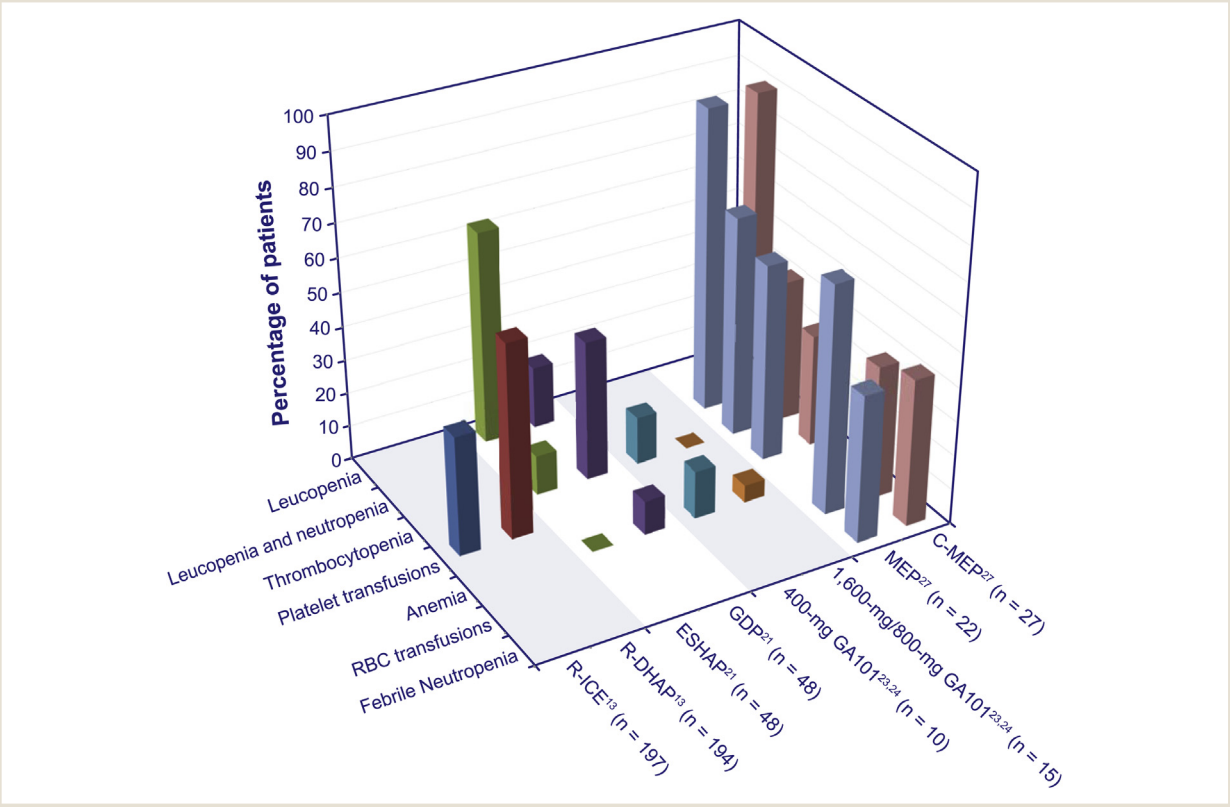
With so few RCTs identified in the R/R DLBCL literature review, we decided to consider therapy assessments in single-arm trials. However, interpreting the relative usefulness of the therapies in such studies is made difficult by a number of factors related to study characteristics and reporting issues. One factor making comparison of single-arm studies difficult is the small number of patients with R/R DLBCL in most of these single-arm studies (< 30). This results in greater variability around measures of central tendency than is seen in studies of larger populations. Another

Table 3 Overall Survival in Noncomparative Studies of Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Regimen	Overall Survival, mo		No. With DLBCL	Reference
	Median	Range		
GDP	27.4 if no CR Not reached for patients with CR ($P = .01$)	NR	70	Hamid et al, 2011[73]
Rituximab plus inotuzumab	10	NR	61	Wagner-Johnston et al, 2011[70]
Gemcitabine plus vinorelbine	12.9	4-54+	22	Papageorgiou et al, 2005[48]
R-GND	3.9	NR	21	Stevens et al, 2011[47]
MiCMA-IGEV (alternating)	12	1-29	20	Giordano et al, 2011[41]
GEPD	Not reached (short follow-up)		13	Kim et al, 2009[38]

Abbreviations: CR = complete response; GDP = gemcitabine, dexamethasone, and cisplatin; GEPD = gemcitabine, etoposide, cisplatin, and dexamethasone; MiCMA-IGEV = mitoxantrone, carboplatin, cytarabine (Ara-C), methylprednisolone (solumedrol) plus ifosfamide, gemcitabine, and vinorelbine; NR = not reported; OS = overall survival; R-GND = rituximab plus gemcitabine, dexamethasone, and cisplatin.

Figure 4 Comparative Studies: Grade 3/4 Hematologic Adverse Events



Note: Blank space indicates the adverse event was not reported.
Abbreviations: C-MEP = carboplatin, mitoxantrone, etoposide, and prednisone; ESHAP = etoposide, methylprednisolone (solumedrol), cytarabine (Ara-C), and cisplatin; GA101 = obinutuzumab; GDP = gemcitabine, dexamethasone, and cisplatin; MEP = mitoxantrone, etoposide, and prednisone; RBC = red blood cell; R-DHAP = rituximab, dexamethasone, high-dose cytarabine (Ara-C), and cisplatin; R-ICE = rituximab, ifosfamide, carboplatin, and etoposide.

limitation with the single-arm studies reviewed is that the most important outcomes, OS and PFS, often were not reported separately for patients with R/R DLBCL. In addition, the type of R/R DLBCL–specific OS and PFS outcomes varied (eg, median, 1-year survival, 5-year survival).

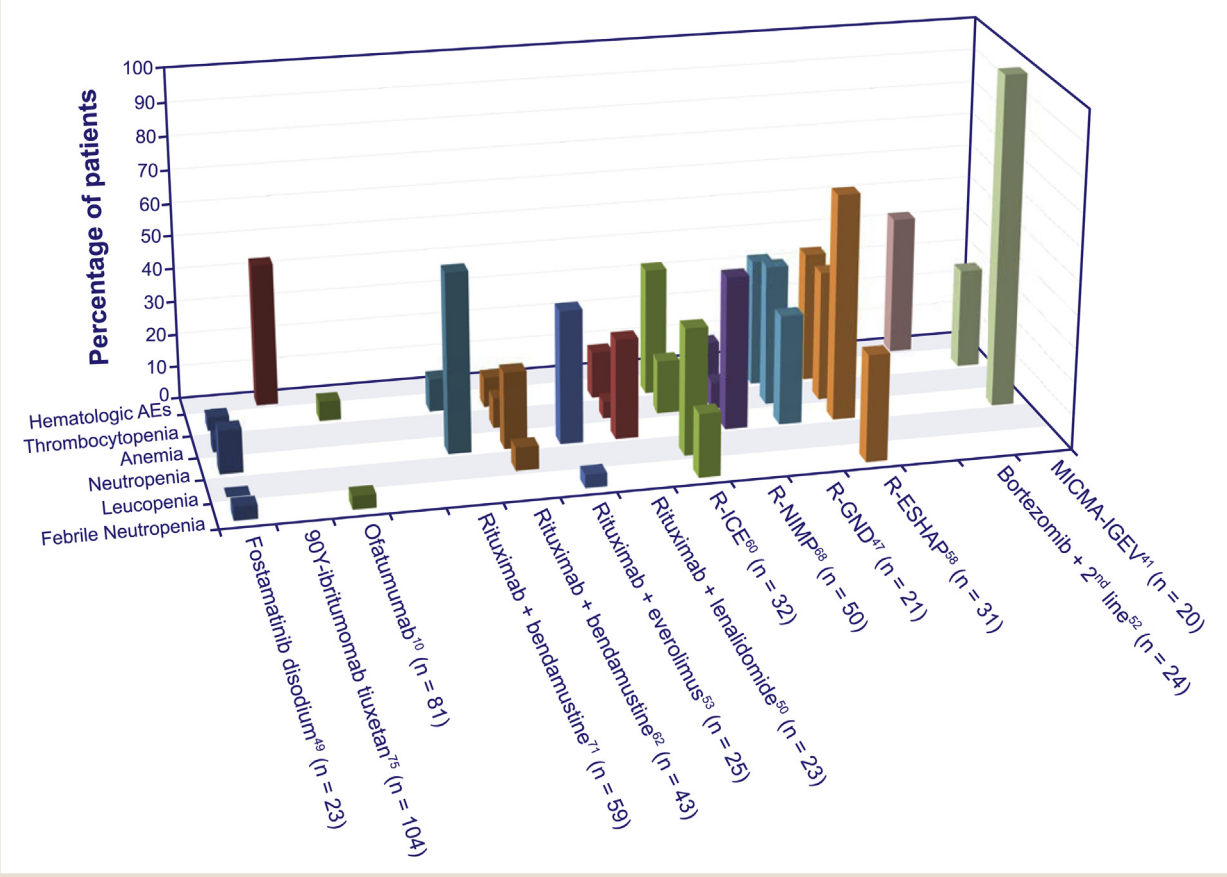
Another factor that makes comparisons among single-arm studies problematic is that although the likelihood of achieving an objective tumor response is typically influenced by whether the patient was previously treated with a given drug or regimen, as well as the response that was obtained previously and how long it was maintained, most of the identified studies did not detail patients' previous treatments or responses. Also, some of these studies predate the availability of rituximab, which has become a standard part of first-line therapy.[14] Previous treatment was likely heterogeneous in most studies because many of the patients had been treated with 2, 3, 4, or more regimens before entering the studies we reviewed.

Comparison of outcomes from single-arm studies might provide insights when the patient populations among studies are similar. However, analysis of outcomes for the single-arm studies by patients' baseline characteristics was not feasible given the limited and variable information provided in publications.

Another challenging issue in evaluating the literature on treatment of R/R DLBCL is that although all the studies included in this review stated that patients had R/R DLBCL, very few of the studies provided definitions for "relapse" or "refractory disease." Among the studies that did, Jerkeman et al[56] defined relapse as disease progression after an initial complete remission, whereas the other 2 studies defined relapse as disease progression after at least a partial response to the previous therapy.[31,68] Similarly, definitions of refractory disease required either not achieving a complete response in 1 study[13] or not achieving a partial response in 2 studies.[31,66] These few studies indicate that the heterogeneity of the population regarding response to previous therapy may be considerable among the larger set of studies for which these terms were not defined.

The evidence gathered in this systematic review suggests that there is a paucity of high-quality comparative evidence regarding treatments used for R/R DLBCL. Response rates reported in the comparative and noncomparative studies for R/R DLBCL varied widely. Although data from the comparative studies could not be evaluated collectively because of a lack of common comparators, the single-arm studies also could not be assessed directly in relation to each other through meta-analysis because the sparse patient data provided precludes adjustment for differences in potentially prognostic patient characteristics. A visual assessment of outcomes from single-arm trials suggests that monotherapies are typically associated

Figure 5 Noncomparative Studies: Grade 3/4 Hematologic Adverse Events



Note: Blank space indicates the adverse event was not reported.
Abbreviations: R-ESHAP = rituximab, etoposide, methylprednisolone (solumedrol), cytarabine (Ara-C), and cisplatin; R-ICE = rituximab, ifosfamide, carboplatin, and etoposide; R-GND = rituximab, gemcitabine, vinorelbine, and liposomal doxorubicin; R-NIMP = rituximab, vinorelbine, ifosfamide, mitoxantrone, and prednisone; MiCMA-IGEV = MiCMA (mitoxantrone, carboplatin, cytarabine [Ara-C], and methylprednisolone [solumedrol]) alternating with IGEV (ifosfamide, gemcitabine, and vinorelbine).

with fewer responses and shorter PFS than multidrug regimens and that regimens with more than 2 drugs may be more effective than 2-drug regimens. Another impression is that rituximab contributes little additional effect to regimens with more than 2 drugs. This interpretation is consistent with outcomes from the single comparative study of ESHAP with or without rituximab.[22] However, the few studies with survival outcomes and the single-arm nature of most of the studies in this review do not allow definitive conclusions regarding the role of rituximab in R/R DLBCL. Nonetheless, rituximab is commonly used in the R/R setting in combination with chemotherapy or as a single agent.

There were also limited data comparing clinical outcomes for patients previously treated with rituximab versus those who were rituximab-naive. Two studies[13,75] reported better clinical outcomes for patients with R/R DLBCL who were naive to rituximab therapy, whereas 1 study found no effect.[63] Determining whether rituximab is useful for R/R DLBCL is complicated by patient factors (eg, age, comorbidities), treatment factors (duration of rituximab therapy), and R/R history (eg, during initial rituximab therapy, during maintenance rituximab therapy, or after stopping rituximab). In this review, the information reported was not sufficient to allow a thorough analysis of rituximab's role in the R/R setting.

Limitations

Because the goal of this review was to summarize data specifically on R/R DLBCL, we excluded studies that did not present outcomes separately for patients with R/R DLBCL. This requirement meant that survival and safety outcomes were not considered when those outcomes were reported only collectively for patient populations with mixed histologic types. Although this may have led to exclusion of studies that are potentially more broadly informative, we considered it important to focus on studies reporting results of new therapies without potential confounding from significantly better or worse performance in non-DLBCL subsets of patients with NHL.

Treatments for Relapsed or Refractory DLBCL Approved by Regulatory Authorities

Although several second-line agents are recommended to treat patients with R/R DLBCL[14], pixantrone is the only drug formally

approved for multiply R/R aggressive NHL, including DLBCL. The pivotal study included patients with complete or partial responses to previous anthracycline therapy. Pixantrone is approved in the European Union[77] but not in the United States. In July 2013, the United Kingdom's National Health Service did not recommend funding pixantrone for this indication.[78] The reasons included low power of the phase III study (the originally planned size was 320 patients not the 140 patients finally included) and nonsignificant treatment differences for complete response (both confirmed and unconfirmed), PFS, and OS for the subset of patients who had received previous rituximab therapy and NHL established as aggressive retrospectively by a central reviewing committee.[79]

The phase II study that led to the pivotal pixantrone study is included in this literature review.[51] Approval in the European Union was based on an open-label phase III study in patients with R/R NHL, including DLBCL (74%), transformed indolent lymphoma, peripheral T-cell lymphoma not otherwise classified, primary anaplastic large-cell lymphoma (null-cell type), and grade 3 follicular lymphoma.[80] The comparator was the physician's choice of treatment. The study was not included in this review because outcomes for the DLBCL subset were not reported separately. In the intent-to-treat population, response rates were significantly higher and PFS was significantly longer for patients treated with pixantrone, but OS was less than 1 year and did not differ significantly between groups. In the subset of 126 patients with aggressive lymphoma, approximately 80% of whom had DLBCL, the group treated with pixantrone had a higher response rate (40.6% vs. 16.1%; $P = .003$) and longer median PFS (5.7 months vs. 2.5 months; $P = .002$) compared with the physician's choice group. Median OS in the aggressive lymphoma subgroup was not assessed in this exploratory analysis.[80]

In an ongoing RCT, pixantrone is currently being studied in combination with rituximab in patients with aggressive NHL; the comparator is gemcitabine plus rituximab.[81]

Conclusion

Although many studies have been conducted to assess the efficacy of various therapeutic regimens in R/R DLBCL, the small number of randomized trials makes it difficult to identify the optimal treatment. Small sample sizes, infrequent reporting of separate OS/PFS outcomes by histologic type, and varying patient characteristics, including limited information on previous treatments and responses, also make comparison of results difficult.

Comparative studies demonstrating relative survival advantages of innovative therapies in patients with R/R DLBCL are needed. In the absence of such robust evidence, currently available information is insufficient to identify any particular well-established optimal therapy for patients with R/R DLBCL, and medical management should be based on individual patient characteristics, concerns regarding medication tolerability, and physicians' experience and familiarity with administering specific regimens. Although many studies of treatments for R/R DLBCL have been conducted and their results published, the paucity of well-designed randomized studies with PFS or OS outcomes and the disappointing long-term outcomes for patients with this condition highlight the substantial unmet medical need for more effective treatments to be developed and for novel therapies to be rigorously assessed in relation to currently available treatments in prospectively designed comparative studies.

Acknowledgments

This work was supported by Sanofi.

Disclosure

This project was funded under a contract with Sanofi. Ann Colosia, PhD; Annete Njue, PhD; Shahnaz Khan, MPH; Rachel Police, MPH; Jianmin Wang, PhD; and James A. Kaye, MD, DrPH, are employees of RTI Health Solutions and provided consulting services to Sanofi. Peter C. Trask, PhD, MPH; Robert Olivares, MD; and Adeline Abbe, MSc, are employees of Sanofi. Farrukh Awan, MD, MS provided consulting services to Sanofi and is supported by a Career Development Award from the Lymphoma Research Foundation. Rodrigo Ruiz-Soto, MD, MSc, was employed by Sanofi at the time of this research.

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Supplemental Appendix

Table A-1 presents the search strategy for PubMed, which was translated into the appropriate syntax for EMBASE and the Cochrane Library.

Table A-1 PubMed Literature Search Strategy for DLBCL, MCL, and Indolent B-Cell Non-Hodgkin Lymphoma

Search Number	Search Terms	Results
Population		
	DLBCL	
1	"Lymphoma, Large B-Cell, Diffuse"[Mesh] OR "diffuse large B-cell lymphoma"[Title/Abstract] OR diffuse large B cell lymphoma*[Title/Abstract] OR "DLBCL"[Title/Abstract] OR "Lymphoma, Large-Cell, Anaplastic"[MeSH] OR "Lymphoma, Primary Cutaneous Anaplastic Large Cell"[MeSH] OR "Aggressive non Hodgkin's lymphoma"[Title/Abstract] OR "Aggressive NHL"[Title/Abstract] OR large B cell lymphoma*[Title/Abstract] OR "diffuse lymphoma"[Title] OR "diffuse non Hodgkin's lymphoma"[Title] OR "diffuse non Hodgkin lymphoma"[Title] OR "large B cell non-Hodgkin's lymphoma"[Title/Abstract] OR "large B cell non-Hodgkin lymphoma"[Title/Abstract] OR Large Cell Lymphoma*[Title/Abstract]	9839
	Mantle Cell Lymphoma	
2	"Lymphoma, Mantle-Cell"[MeSH] OR "mantle-cell lymphoma"[Title/Abstract] OR mantle cell lymphoma*[Title/Abstract] OR "MCL"[Title/Abstract] OR mantle zone lymphoma*[Title/Abstract] OR "Centrocytic lymphoma"[Title/Abstract]	5874
	Indolent B-Cell Non-Hodgkin Lymphoma	
3	"indolent b-cell lymphoma"[Title/Abstract] OR indolent b cell lymphoma*[Title/Abstract] OR "Lymphoma, B-Cell, Marginal Zone"[MeSH] OR extranodal marginal zone lymphoma*[Title/Abstract] OR "mucosa-associated lymphatic tissue"[Title/Abstract] OR "mucosa associated lymphatic tissue"[Title/Abstract] OR MALT lymphoma*[Title/Abstract] OR nodal marginal zone lymphoma*[Title/Abstract] OR splenic marginal zone lymphoma*[Title/Abstract] OR lymphoplasmacytic lymphoma*[Title/Abstract] OR "Waldenstrom Macroglobulinemia"[MeSH] OR "Waldenstrom macroglobulinemia"[Title/Abstract] OR "Waldenstrom macroglobulinaemia"[Title/Abstract] OR "Waldenstrom's macroglobulinemia"[Title/Abstract] OR "Waldenstrom's macroglobulinaemia"[Title/Abstract] OR "Lymphoma, Follicular"[MeSH] OR follicular lymphoma*[Title/Abstract] OR follicular non hodgkin lymphoma*[Title/Abstract] OR "follicular NHL"[Title/Abstract] OR "Leukemia, Lymphocytic, Chronic, B-Cell"[MeSH] OR "b-cell chronic lymphocytic leukemia"[Title/Abstract] OR b cell chronic lymphocytic leukemia*[Title/Abstract] OR small lymphocytic lymphoma*[Title/Abstract] OR indolent b-cell non-hodgkin's lymphoma*[Title/Abstract] OR "mucosa associated lymphoid tissue"[Title/Abstract] OR "Indolent non Hodgkin's lymphoma"[Title/Abstract] OR "Indolent NHL"[Title/Abstract] OR "giant follicle lymphosarcoma"[Title/Abstract] OR "giant follicular blastoma"[Title/Abstract] OR "giant follicular lymphoblastoma"[Title/Abstract] OR "Lymphoplasmacytic leukaemia"[Title/Abstract] OR Lymphocytic Lymphoma*[Title/Abstract] OR "Lymphoplasmacytic lymphoma"[Title/Abstract] OR "Waldenstrom's disease"[Title/Abstract] OR "Waldenstroem's disease"[Title/Abstract] OR "Extranodal marginal zone B-cell lymphoma of MALT type"[Title/Abstract] OR "Nodal marginal zone B-cell lymphoma"[Title/Abstract] OR "Splenic marginal zone B-cell lymphoma"[Title/Abstract] OR "Lymphoplasmacytic lymphoma"[Title/Abstract]	15,184
4	No. 1 OR No. 2 OR No. 3	27,964

Table A-1 Continued

Search Number	Search Terms	Results
Interventions		
5	"Drug Therapy"[MeSH] OR "Biological Therapy"[MeSH] OR "Combined Modality Therapy"[MeSH] OR "Hematopoietic Stem Cell Transplantation"[MeSH] OR "Immunotherapy"[MeSH] OR "immunochemotherapy"[Title/Abstract] OR "Molecular Targeted Therapy"[MeSH] OR targeted therap*[Title/Abstract] OR "induction therapy"[Title/Abstract] OR "pharmacotherapy"[Title/Abstract] OR "pharmacotherapies"[Title/Abstract] OR chemotherap*[Title/Abstract] OR "Chemoradiotherapy"[MeSH] OR "Salvage Therapy"[MeSH]	750,621
Study Design (Clinical Trials)		
6	"Clinical Trial, Phase II"[Publication Type] OR "Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Multicenter Study"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Clinical Trials, Phase II as Topic"[MeSH] OR "Clinical Trials, Phase III as Topic"[MeSH] OR "Clinical Trials, Phase IV as Topic"[MeSH] OR "Controlled Clinical Trials as Topic"[MeSH] OR "Multicenter Studies as Topic"[MeSH] OR clinical trial*[Title/Abstract] OR "randomized"[Title/Abstract] OR "randomized"[Title/Abstract] OR "randomization"[Title/Abstract] OR "randomisation"[Title/Abstract] OR "phase II"[Title] OR "phase 2"[Title] OR "phase III"[Title] OR "phase 3"[Title] OR "phase IV"[Title] OR "phase 4"[Title] OR "phase I/II"[Title] OR "phase 1/2"[Title] OR "phase II/III"[Title] OR "phase 2/3"[Title] OR "placebo-controlled"[Title/Abstract] OR "random allocation"[Title/Abstract] OR "double blind"[Title/Abstract] OR "double blinded"[Title/Abstract] OR "double masked"[Title/Abstract] OR "single blind"[Title/Abstract] OR "single blinded"[Title/Abstract] OR "single masked"[Title/Abstract] OR "single arm"[Title/Abstract] OR "uncontrolled clinical trial"[Title/Abstract] OR "uncontrolled clinical study"[Title/Abstract] OR "open label"[Title/Abstract] OR "non-randomized"[Title/Abstract] OR "clinical study"[Title/Abstract]	582,167
7	No. 4 AND No. 5 AND No. 6	2006
Exclusion Terms		
8	"Comment"[Publication Type] OR "Editorial"[Publication Type] OR "Letter"[Publication Type] OR "Case Reports"[Publication Type] OR "Guideline"[Publication Type] OR "Guidelines as Topic"[MeSH] OR case report*[Title/Abstract] OR "case series"[Title/Abstract] OR "case study"[Title/Abstract] OR "case studies"[Title/Abstract] OR retrospective stud*[Title/Abstract] OR "Retrospective Studies"[MeSH] OR "prognostic"[Title/Abstract]	1,701,360
9	"Animals"[MeSH] NOT "Humans"[MeSH]	1,423,331
Total		
10	**No. 7 NOT (No. 8 OR No. 9)**	**1378**

Note: Search limits were publications in English from 1997 to present.
Abbreviation: DLBCL = diffuse large B-cell lymphoma.

Efficacy and Safety in Relapsed/Refractory DLBCL

Table A-2 presents the quality assessments of the 4 RCTs. The treatment groups within all 4 trials were similar at baseline. Two of the studies reported being single blind with no further explanation,[1,2] but given the nature of the disease and treatments, presumably the assessor was blinded. The third study gave no information regarding blinding.[3] The fourth study was reported in conference abstracts, and no details were given about masking.[4,5] Information on dropout rates was presented in 2 of the RCTs[1,3] but not in the other 2 RCTs.[2,4,5]

Table A-2 Quality Assessment of Studies in DLBCL

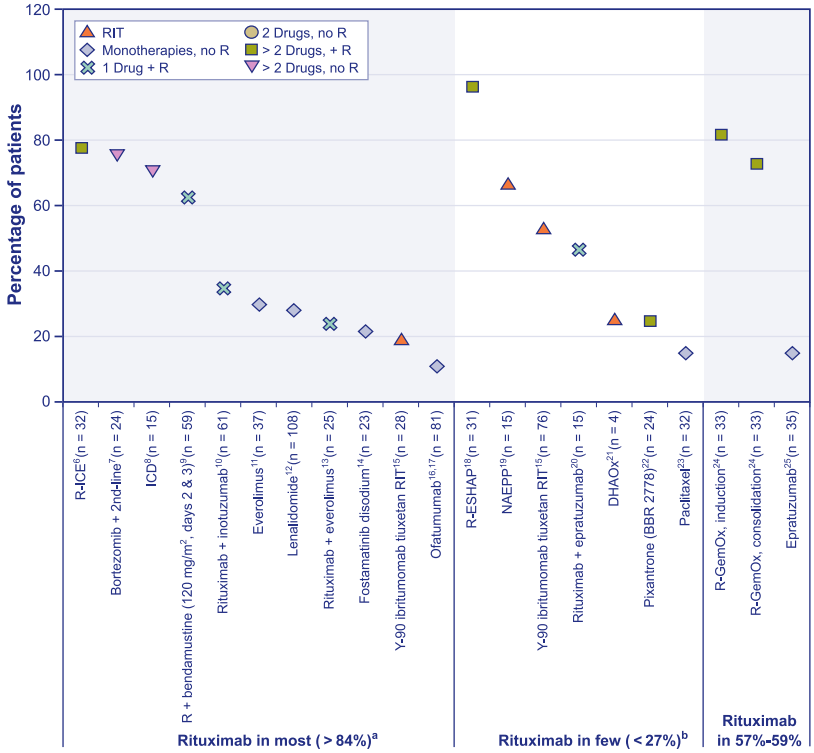
Study	Quality Assessment Query	Trial Quality	Notes
Aribi et al, 2010[1]	Was randomization carried out appropriately?	Not clear	No details on method "Patients were randomly divided into 2 equal groups"
	Was the concealment of treatment allocation adequate?	Yes	Single-blind, presumably the assessor and not the investigator
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Table 1 statistically compares patient characteristics and clinical presentations, and no differences were significant
	Were care providers, participants and outcome assessors blind to treatment allocation	No	Single blind; presume that assessor was blinded and not physician or patient
	Were there any unexpected imbalances in dropouts between groups?	No	Table 3: patients lost to follow-up, not significantly different between groups
	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes noted in the methods were reported in the article
	Did the analysis include an ITT analysis?	Yes	96 patients enrolled; analysis is on 96 patients
	If ITT analysis used, was this appropriate and were appropriate methods used to account for missing data?	Not clear	No details on how missing data were handled
Aviles et al, 2010[2]	Was randomization carried out appropriately?	Not clear	No details on method: "They were randomized to receive rituximab or not"
	Was the concealment of treatment allocation adequate?	Not clear	Lack of masking description suggests open-label study
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	"No differences were observed between the 2 arms among clinical and laboratory characteristics (Table 1)"
	Were care providers, participants, and outcome assessors blind to treatment allocation	No	Single blind; presume that assessor was blinded and not physician or patient
	Were there any unexpected imbalances in dropouts between groups?	Not clear	No information on dropouts, including whether there were any
	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes noted in the methods were reported in the article
	Did the analysis include an ITT analysis?	Yes	100 patients were enrolled; analysis is on 100 patients
	If ITT analysis used, was this appropriate and were appropriate methods used to account for missing data?	Yes	"Patients without progression or relapse who were still alive were censored at the date of last contac:"
Gisselbrecht et al, 2010[3]	Was randomization carried out appropriately?	Not clear	No details on method. "On an intent-to-treat basis, 396 patients were randomly assigned (202 patients to the R-ICE arm and 194 patients to the R-DHAP arm)"
	Was the concealment of treatment allocation adequate?	Not clear	Lack of masking description suggests open-label study
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Table 1 statistically compares patient characteristics and clinical presentations, and no differences were significant
	Were care providers, participants, and outcome assessors blind to treatment allocation?	Not clear	No text on masking
	Were there any unexpected imbalances in dropouts between groups?	No	Figure 1 shows similar numbers of patients withdrawn during induction and before the second randomization
	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes noted in the methods were reported in the article
	Did the analysis include an ITT analysis?	Yes	13 (3%) patients were misclassified as having DLBCL but were included in the analysis per ITT
	If ITT analysis used, was this appropriate and were appropriate methods used to account for missing data?	Not clear	There was no description of how missing data were handled

Table A-2 Continued

Study	Quality Assessment Query	Trial Quality	Notes
Morschhauser et al, 2011[4] and Cartron et al, 2010[5]	Was randomization carried out appropriately?	Not clear	No details on method. "Patients were randomized to receive…"
	Was the concealment of treatment allocation adequate?	Not clear	No details on masking
	Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	"Baseline patient characteristics were similar for both cohorts (Table 1)"
	Were care providers, participants, and outcome assessors blind to treatment allocation?	Not clear	No details on method
	Were there any unexpected imbalances in dropouts between groups?	Not clear	No information on dropouts, including whether there were any
	Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Information was limited in these conference abstracts
	Did the analysis include an ITT analysis?	Yes	40 patients were enrolled; analysis is on 40 patients
	If ITT analysis used, was this appropriate and were appropriate methods used to account for missing data?	Not clear	No details on methods or missing data

Abbreviations: DLBCL = diffuse large B-cell lymphoma; ITT = intention-to-treat; R-DHAP = rituximab plus dexamethasone, cytarabine (Ara-C), and cisplatin; R-ICE = rituximab plus ifosfamide, carboplatin, and etoposide.

Figure 1 Objective Response Rates in Noncomparative Studies by Rituximab History



[a]The proportion of patients with prior rituximab therapy was 100% in 6 studies, 96%-98% in 4 studies, and 85%-88% in only 2 studies.
[b]The proportion of patients with prior rituximab therapy was 26% in only 1 study and 7% in 1 other study; none of the patients received rituximab in the remaining studies.

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