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CLINICAL TRIALS AND OBSERVATIONS

Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis

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Key Points

- A subset of DHL patients may be cured, and some patients may benefit from intensive induction.
- Further investigations into the roles of SCT and novel agents are needed.

Patients with double-hit lymphoma (DHL), which is characterized by rearrangements of MYC and either BCL2 or BCL6, face poor prognoses. We conducted a retrospective multicenter study of the impact of baseline clinical factors, induction therapy, and stem cell transplant (SCT) on the outcomes of 311 patients with previously untreated DHL. At median follow-up of 23 months, the median progression-free survival (PFS) and overall survival (OS) rates among all patients were 10.9 and 21.9 months, respectively. Forty percent of patients remain disease-free and 49% remain alive at 2 years. Intensive induction was associated with improved PFS, but not OS, and SCT was not associated with improved OS among patients achieving first complete remission ($P = .14$). By multivariate analysis, advanced stage, central nervous system involvement, leukocytosis, and LDH >3 times the upper limit of normal were associated with higher risk of death. Correcting for these, intensive induction was associated with improved OS. We developed a novel risk score for DHL, which divides patients into high-, intermediate-, and low-risk groups. In conclusion, a subset of DHL patients may be cured, and some patients may benefit from intensive induction. Further investigations into the roles of SCT and novel agents are needed. (*Blood*. 2014;124(15):2354-2361)

Introduction

Rearrangement of the *MYC* proto-oncogene, classically described in Burkitt lymphoma (BL), may occur in other B-cell lymphomas, and confers an adverse prognosis in patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[1,2] Cases in which *MYC* rearrangement coincides with other recurring translocations

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of either *BCL2* or *BCL6* have been termed "double-hit" lymphomas (DHL) on the basis of their dual genetic insults, or "triple-hit" lymphoma (THL) if all 3 rearrangements coexist.[3,4] Presently, it remains unclear whether patients with THL fare differently from those with DHL.[5,6] DHL and THL have been reported almost exclusively among DLBCL and B-cell lymphoma unclassifiable with features intermediate between DLBCL and BL (BCLU) histologies.[5] DHL, as defined by cytogenetic criteria (karyotype or fluorescence in situ hybridization [FISH]), constitutes anywhere from 3% to 32% of cases of DLBCL in individual case series,[7,8] but its true frequency is likely 5% to 10% based on collective data.[9]

Multiple retrospective series suggest that patients with DHL, as defined by FISH, face very poor prognoses when treated with R-CHOP, with a median overall survival (OS) of 12 months or less.[10-14] These studies furthermore suggest that, compared with patients with non-DHL DLBCL, DHL patients more frequently present with extranodal involvement, elevated lactate dehydrogenase (LDH) levels, central nervous system (CNS) involvement, and higher international prognostic index (IPI) scores.[15] Most of these studies comprised between 10 and 28 patients with DHL, making it difficult to form generalized conclusions about disease features, prognosis, and treatment.

The role of intensified induction regimens for patients with DHL is of interest, given the well-defined role of these regimens in patients with BL[16,17]; however, their efficacy in DHL remains unknown. Retrospective analyses thus far have not identified outcomes superior to those observed with R-CHOP when using intensive regimens such as R-Hyper CVAD/MA (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, cytarabine) or R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide cytarabine).[15,18,19] There are both randomized[20,21] and single-arm phase 2 data[22] suggesting that intensive induction and/or consolidation therapy may improve outcomes for selected patients with DLBCL, though none have assessed outcome with respect to DHL. Similarly, consolidation with either high-dose chemotherapy with autologous stem cell transplant (HDT-ASCT)[23] or allogeneic (allo) stem cell transplant (SCT),[24] may also improve outcomes in patients with aggressive B-cell malignancies, although the role of each in DHL remains undefined.

Given the limitations of existing data, and the poor outcomes observed for patients with DHL treated with R-CHOP, we sought to (1) further characterize the clinical features of DHL, (2) evaluate whether intensive induction therapy and/or frontline SCT consolidation is associated with improved outcomes in DHL, and (3) determine whether current prognostic models for DLBCL are applicable to DHL. We performed a large multicenter retrospective analysis of patients with DHL (defined by FISH) to address these questions.

Patients and methods

We conducted a multicenter, retrospective analysis of patients diagnosed with DHL and treated across 23 North American academic medical centers. The study protocol was approved by the institutional review board of each institution. All patients were adults (age >18 years) diagnosed between January 2000 and December 2012 with B-cell lymphoma carrying a *MYC* rearrangement, as detected by FISH or conventional cytogenetics, along with either *BCL2* rearrangement or *BCL6* rearrangement, or both. Neither expression of *MYC* and/or *BCL2* by immunohistochemistry (IHC) nor other FISH-detected *MYC* abnormalities (eg, gain of copy number) were included as eligibility criteria. Patients were excluded for known human immunodeficiency virus (HIV), Burkitt lymphoma/leukemia (but not Burkitt-like lymphoma), and for previous treatment (but not diagnosis) of indolent non-Hodgkin lymphoma (NHL).

The clinical variables collected are provided in supplemental Table 1; patients were not excluded solely on the basis of missing data. Data for 355 patients were submitted, and 44 were excluded by eligibility criteria, leaving 311 for the final analysis. Pathology was reviewed by hematopathologists at participating institutions (though not centrally), and no data regarding toxicity or supportive measures were collected. All clinical management decisions and response evaluations were performed independently by the patients' treating physicians. Approximately 159 patients included in this analysis were included in previous single-center analyses,[8,12,19,25-28] though each differed from the current report in terms of eligibility criteria and research questions.

Statistical analyses

Baseline (pretreatment) and treatment variables were collected, along with dates of first progression, last follow-up, and death. Univariate analyses (UVA) for OS were performed using each of the pretreatment variables evaluated. OS was computed from the date of diagnosis to the date of either death or last documented follow-up. Progression-free survival (PFS) was calculated from the date of diagnosis to either progression or death from any cause. Survival analyses were performed regardless of duration or type of therapy received. PFS and OS rates were estimated using the Kaplan-Meier method, and differences were assessed with the log-rank (Mantel-Cox) test. Bivariate associations between pretreatment clinical and laboratory factors and survival were assessed. Variables with a $P < .05$ on UVA were included in the stepwise multivariate Cox proportional hazards model. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated. To evaluate the impact of induction regimen, the Cox proportional hazards model was recalculated with the addition of induction regimen as a variable. Significant factors identified in the multiple variable analysis (MVA) were used to construct a prognostic model and develop a candidate prognostic score for DHL. The presence of each variable was assigned one point, and the sum of the variables constituted the DHL prognostic score. Kaplan-Meier survivals curves were generated, and UVA was performed, with Prism software (GraphPad, LaJolla, CA); multivariate analyses were performed with Stata version 12.1 (StataCorp, College Station, TX). Differences in categorical data were calculated using the Fisher exact test with significance defined as $P \leq .05$. All P values are two-tailed.

Results

Baseline characteristics

Baseline patient characteristics are presented in Table 1. Median year of diagnosis was 2010, nearly two-thirds of patients had stage IV disease, and at least 45% of patients with available data presented with B symptoms. Among those who underwent CNS staging, approximately 10% had involvement at the time of diagnosis, but nearly one-third of patients did not have reported baseline CNS staging. Bone marrow involvement and extranodal disease (beyond marrow involvement) were present in 41% and 59% of patients, respectively.

The most common histologies were DLBCL (50%) and BCLU (48%). Most patients (87%) had *BCL2* rearrangements, 5% had *BCL6* rearrangements, and 7% had both. LDH was elevated in more than three-quarters of patients, and one-third had an LDH >3 times the upper limit of normal (ULN). White blood cell (WBC) levels was elevated in nearly one-quarter, and differential data were not available. Where tested, nearly all tumors (93%) were positive for CD20 and CD10, consistent with germinal center (GC) derivation (rates of GC origin were not significantly different when analyzed among

Table 1. Baseline characteristics of patients with DHL (N = 311)

	n (%)
Patient characteristics	
Median age at dx (range)	60 (19-87)
Male	187 (61)
Median year of dx	2010
Race/Ethnicity	
White (non-Hispanic)	225 (72)
Black	9 (3)
Asian	7 (2)
Hispanic	19 (6)
Other/unknown	51 (16)
ECOG PS	
0	79 (25)
1	142 (46)
2	65 (21)
3	15 (5)
4	6 (2)
NA	4 (1)
Median BSA, m^2 (range)	2.0 (1.37-2.80)
Median BMI (range)	27.4 (18.1-47.0)
Prior indolent NHL	67 (22)
Disease characteristics	
Stage	
I	20 (6)
II	36 (12)
III	49 (16)
IV	206 (65)
B symptoms	
Present	139 (45)
Absent	103 (33)
NA	69 (22)
Extranodal sites*	
0	123 (40)
1	100 (32)
2	57 (18)
3	21 (7)
4 or more	9 (3)
NA	1 (<1)
Bone marrow involvement	
Positive	129 (41)
Negative	162 (52)
NA	20 (6)
CNS involvement*	
Positive	23 (7)
Negative	185 (59)
NA	102 (33)
Pathology/laboratory characteristics	
Histology	
DLBCL	154 (50)
BCLU	150 (48)
FL	7 (2)
Partner translocation	
BCL2	270 (87)
BCL6	16 (5)
Both BCL2 and BCL6	25 (8)
Cell of origin	
GCB†	181 (58)
Non-GCB	27 (9)
NA	102 (33)
Median LDH level, U/L (range)	545 (120-42 000)
LDH level relative to ULN	
>ULN	236 (76)
>3× ULN	103 (33)
Median WBC, 10^3/mL (range)	6.8 (1-355)
WBC relative to ULN	
Elevated	68 (22)
Normal	174 (56)
NA	69 (22)
Median albumin level, g/dL (range)	3.5 (2-5.1)
CD10 status	
Positive†	255 (82)
Negative	18 (6)
NA	38 (12)
CD20 status	
Positive	269 (86)
Negative	10 (3)
NA	32 (10)

Dx, diagnosis; ECOG PS, Eastern Cooperative Group performance status; BSA, body surface area; BMI, body mass index; NHL, non-Hodgkin lymphoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; BCLU, B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell origin; LDH, lactate dehydrogenase; ULN, upper limit of normal; NA, not available.

*CSF vs parenchymal involvement not obtained.

†Discrepancy between rates of GCB and CD10 positivity are the result of more missing data with respect to cell of origin.

only those with DLBCL [χ^2, $P = .25$]). Data were missing for one-half or more of patients for other IHC markers.

Treatment, response, and use of SCT

Data regarding treatment variables are provided in Table 2. Of those with reported data, 95% received rituximab as part of induction. R-CHOP was the most frequently used induction regimen (32%) followed by R-HyperCVAD/MA and DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) in 21% each. R-CODOX-M/IVAC was administered to 14% of patients. Among all patients, the median number of induction chemotherapy cycles was 5 (range 0-9). Those with DLBCL (χ^2, $P = .007$) and those over age 60 (χ^2, $P = .001$) were more likely to receive R-CHOP or DA-EPOCH-R compared with R-HyperCVAD/MA or R-CODOX-M/IVAC, but Eastern Cooperative Oncology Group (ECOG) performance status (PS; 0-1 vs 2-4) did not affect choice of treatment. Response rates by induction regimen are provided in Figure 1. DA-EPOCH-R resulted in significantly higher rates of CR compared with R-CHOP, R-CODOX-M/IVAC, or "other/multiple" regimens. A total of 83 patients underwent SCT at any time, 39 of whom had SCT (28 HDT-ASCT; 11 allo-SCT) in first complete remission (CR) and 14 of whom had SCT during first response, but not in CR (eg, in partial response). Of 154 patients with documented progression, 106 were treated with salvage chemotherapy, with RICE (rituximab, ifosfamide, carboplatin, etoposide) being the most commonly used (47%).

Outcomes

The median duration of follow-up for all living patients was 23 months (range, 1-126). A total of 118 patients (38%) were alive without progression at last follow-up, and 151 patients have died. The median PFS and OS rates for the entire cohort were 10.9 and 21.9 months, respectively (Figure 2A), and the PFS and OS rates at 2 years were 40% and 49%, respectively. Figure 2B-C shows PFS and OS rates by induction regimen, whereas Figure 2D-E shows all patients receiving any of the 3 intensive regimens pooled together, compared with R-CHOP. Although complete PFS data were missing for 69 patients (OS data available for all 311 patients), a significant

Table 2. Treatment patterns (N = 311)

	n (%)
Induction regimen	
R-CHOP	100 (32)
R-Hyper-CVAD	65 (21)
DA-EPOCH-R	64 (21)
R-CODOX-M/IVAC	42 (14)
R-ICE	9 (3)
Other/multiple	31 (10)
Rituximab included	
Yes	268 (86)
No	15 (5)
NA	27 (9)
Median # Cycles administered (range)	5 (0-9)
CNS prophylaxis	
None	130 (42)
MTX	102 (33)
Ara-C	6 (2)
Both	66 (21)
NA	7 (2)
Stem cell transplantation	
At any time	83 (27)
In first CR	53 (17)
Autologous SCT in first CR	39 (13)
Allogeneic SCT in first CR	14 (5)
Salvage chemotherapy	
R-ICE	50 (16)
R-ESHAP	6 (2)
R-DHAP	2 (<1)
Other	48 (15)
NA	203 (65)

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-Hyper CVAD, rituximab, cyclophosphomide, vincristine, doxorubicin, dexamethasone, alternating with methotrexate and cytarabine; R-CODOX-M/IVAC, rituximab, cyclophosphamide, vincristine, dexamethasone, methotrexate, ifosfamide, etoposide, cytarabine; R-ICE, rituximab, ifosfomie, carboplatin, etoposide; NA, not available; CNS, central nervous system; MTX, methotrexate; Ara-C, cytarabine; CR, complete remission; R-ESHAP: rituximab, etoposide, methylprednisolone, cytarabine, cisplatin; R-DHAP: rituximab, dexamethasone, cytarabine, cisplatin.

difference in PFS was observed between patients receiving frontline R-CHOP compared with those receiving any of the 3 intensive induction regimens evaluated (median PFS 7.8 vs 21.6 months; $P = .001$). With respect to R-CHOP, each intensive regimen was associated with significantly improved PFS (Hyper CVAD, $P = .001$; CODOX-M/IVAC, $P = .036$; DA-EPOCH-R, $P = .0463$), but no difference was observed comparing intensive regimens with one another (data not shown).

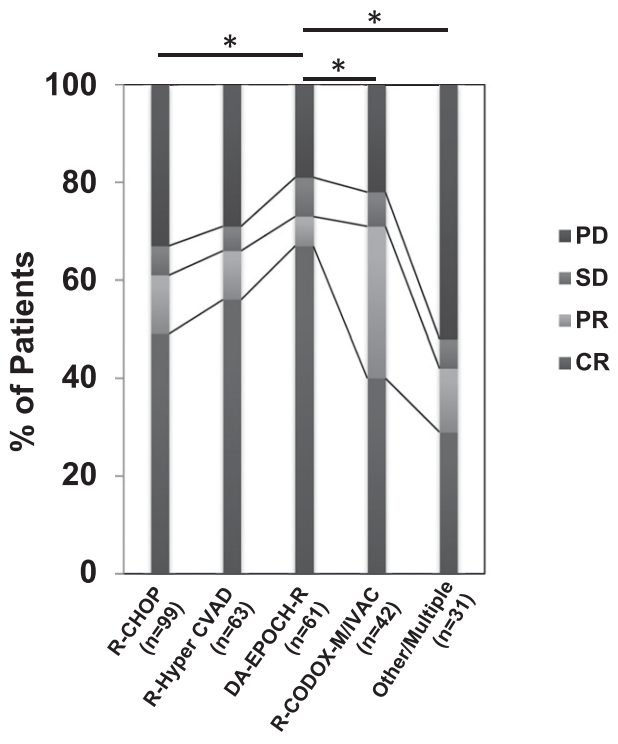
Among patients who achieved a CR to frontline therapy, median OS was similar for those who were observed (103 months) and those who underwent consolidation SCT of any type (median OS not reached; $P = .14$; Figure 3A). Median OS was not reached for patients who received either auto- or allo-SCT in first CR ($P = .302$).

Among patients presenting with CNS involvement, the median OS was significantly inferior to that of patients confirmed to be free of CNS disease at diagnosis (6 vs 36 months; $P < .0001$). Among patients without CNS involvement identified at diagnosis, the use of MTX-containing CNS prophylaxis (either intravenous or intrathecal) was associated with a median OS of 45 months, compared with 14 months in patients who did not receive CNS-directed therapy ($P = .06$; Figure 3B). Patients with relapsed/refractory disease faced a dismal overall prognosis, though salvage therapy was associated with a median OS of 17 months compared with 8 months for those not known to have received salvage therapy ($P < .0001$; Figure 3C).

Univariate/multivariate analyses and prognostic modeling

Each of the variables collected was evaluated by UVA with respect to impact on OS. Data were missing for >25% of patients for certain laboratory values (hemoglobin level and platelet count), IHC results (CD5, CD19, CD22, CD30, CD45, CD79a, and *MYC*), and FISH/cytogenetic features (*MYC* gain of copy [GOC], *BCL2* GOC, *BCL6* GOC), so these factors were excluded from multivariate modeling. Each of the aforementioned IHC results was evaluated by UVA, and none were significant. Of the remaining variables, the following were found to predict inferior OS: age ≥60 years, ECOG performance status 2 to 4, leukocytosis (WBC >10 000/uL), hypoalbuminemia, LDH >3× ULN, presence of "B" symptoms, >1 site of extranodal involvement, advanced Ann Arbor stage, bone marrow involvement, and CNS involvement (Table 3). OS was not affected by histology (DLBCL vs BCLU, $P = .33$), partner rearrangement (BCL2 vs BCL6, $P = .537$; BCL2 vs BCL6 vs THL, $P = .677$), treatment era (2009 and earlier vs 2010 and later, $P = .166$), preexisting indolent NHL (absent vs present, $P = .842$) or cell of origin, whether evaluated among all patients ($P = .138$) or only those with DLBCL ($P = .195$).

The 10 variables that affected OS on UVA were incorporated into the MVA. Factors associated with increased risk of death on MVA were leukocytosis, LDH >3× ULN, advanced Ann Arbor stage, and CNS involvement (Table 3). In an exploratory analysis, we added the variable of treatment (R-CHOP vs intensive induction) and found that intensive induction therapy was associated with improved survival after adjusting for other risk factors, with a hazard ratio of 0.53 (95% CI 0.29-0.98, $P = .042$).



* p<0.05 for CR rate by Fisher's exact test, two-tailed.

Figure 1. Response rates by induction regimen. *$P < .05$ for CR rate by Fisher exact test, 2-tailed.

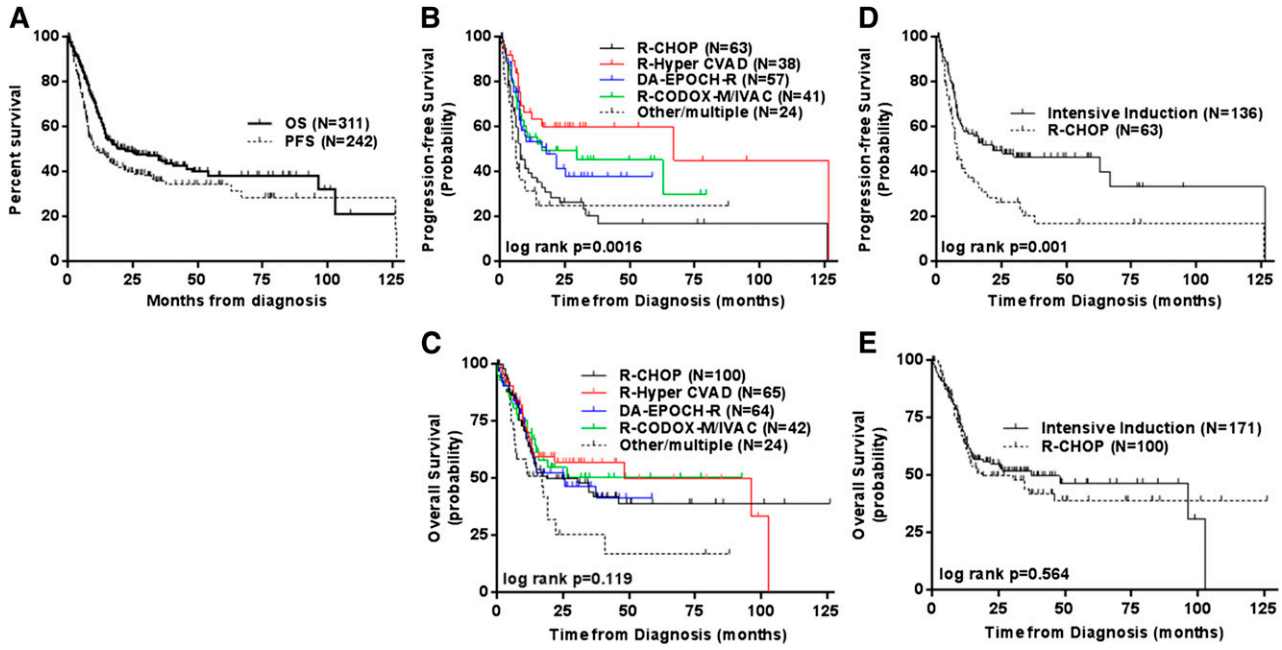


Figure 2. Comparison of long-term, progression-free, and overall survival. Kaplan-Meier curves comparing the long-term (A) progression-free survival (PFS) and overall survival (OS) of the entire cohort; PFS (B) and OS (C) by induction regimen; PFS (D) and OS (E) comparing R-CHOP with other intensified induction regimens (ie, DA-EPOCH, Hyper CVAD, and CODOX/M-IVAC).

We then used the pretreatment variables that were significant on MVA to build and evaluate a novel prognostic scoring system. Because the HR of each variable was similar (1.59-2.00), one point was assigned to each. This model was particularly effective at identifying a favorable-risk population, though cohorts with 2, 3, or 4 points by this model did not have significantly different OS curves from one another (data not shown). We therefore categorized patients into low-risk (0 points), intermediate risk (1 point), and high risk (2 or more points). Of 201 patients with sufficient evaluable data, 14 (7%) were characterized as low risk, 66 (33%) as intermediate risk, and 121 (60%) as high risk. This DHL Prognostic Index (DPI) resulted in excellent discrimination of OS curves for this population, with 2-year estimated OS rates of 91%, 59%, and 41% in the 3 risk groups, respectively (Figure 4A). By comparison, risk stratification by means of the conventional international prognostic index (IPI[29]) and the revised IPI (R-IPI[30]) are demonstrated in Figure 4B-C.

Discussion

The present analysis represents the largest and most comprehensive effort to examine patients with DHL. We demonstrated that intensive induction regimens may be associated with improved response rate,

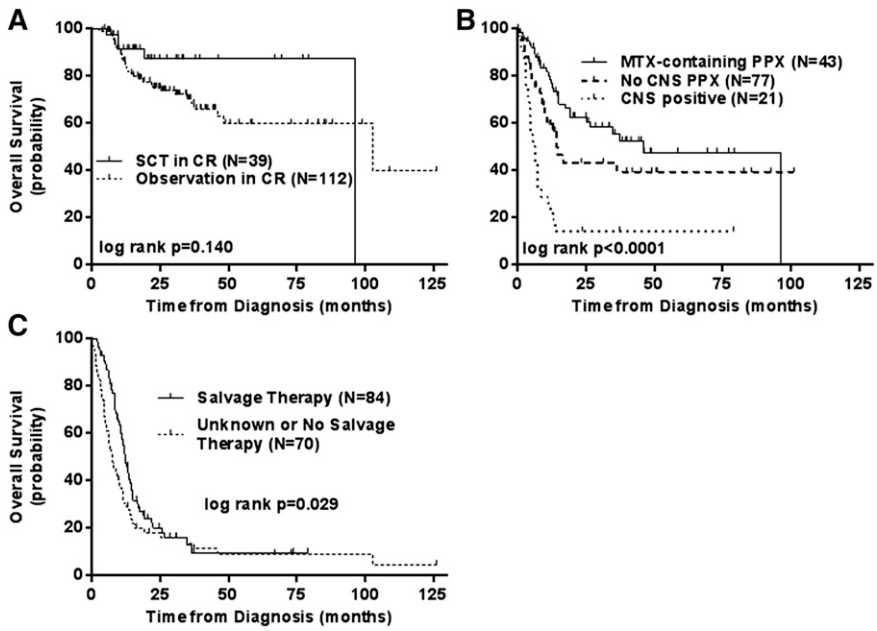


Figure 3. Overall survival by SCT versus observation in first complete remission. Kaplan-Meier curves demonstrating overall survival (OS) by (A) use of SCT compared with observation among those in first complete remission (CR); OS by (B) those who were positive for central nervous system (CNS) involvement at the time of diagnosis compared with those who did and did not receive CNS-directed prophylaxis (PPX); and OS for (C) those with relapsed/refractory disease based on whether salvage therapy was administered (those who were not known to receive salvage therapy are included with those confirmed to have not received salvage therapy).

Table 3. Prognostic factors with associated hazard ratios and *P* values, by both univariate and multivariate analyses

Variable	Risk factor	Reference univariate analysis	Hazard ratio (95% CI)	*P* value
Age	≥60	<60	1.622 (1.177, 2.234)	.003
ECOG PS	2-4	0-1	1.772 (1.304, 2.805)	.001
WBC	$\geq 10^3$	$<10^3$	2.249 (1.694, 4.349)	<.001
Albumin	<4	≥4	1.864 (1.318, 3.026)	.001
LDH	>3× ULN	≤3× ULN	1.907 (1.131, 2.609)	.011
B symptoms	Present	Absent	1.587 (1.083, 2.414)	.019
Extranodal disease	>1 site	0-1 site	1.518 (1.099, 2.294)	.014
Ann Arbor Stage	3-4	1-2	2.607 (1.373, 3.138)	.001
Bone marrow involvement	Positive	Negative	1.906 (1.357, 2.851)	<.001
CNS involvement	Present	Absent	4.700 (3.763, 24.77)	<.001
Multivariate analysis				
WBC	$\geq 10^3$	$<10^3$	1.710 (1.001, 2.923)	.05
LDH	>3× ULN	≤3× ULN	1.727 (1.000, 3.018)	.05
Ann Arbor Stage	3-4	1-2	1.585 (1.351, 3.138)	.014
CNS involvement	Present	Absent	2.000 (1.169, 3.423)	.011

ECOG PS, Eastern Cooperative Oncology Group performance status; WBC, white blood cell count, in 10^3 cells/mL; LDH, lactate dehydrogenase, in U/L; CNS, central nervous system; ULN, upper limit of normal.

PFS, and, when correcting for adverse risk factors, OS. Although consolidative SCT in first CR was not associated with improved OS, a difference may have emerged with a larger cohort. Notably, with respect to incidence of all IPI and DPI risk factors, there was no difference between patients who underwent SCT in first CR and those who were observed in first CR (all χ^2 $P > .18$).

By MVA, adverse factors for OS at diagnosis include leukocytosis, LDH >3× ULN, advanced Ann Arbor stage, and CNS involvement. These findings suggest that a significant minority of DHL patients may be cured of their disease, with a 2-year PFS and OS in our population of 40% and 49%, respectively. We generated a novel risk index, the DPI, that stratified DHL patients into low-, intermediate-, and high-risk groups. Most patients (60%) were high risk, but 7% were in the low-risk group and had excellent OS. Intermediate-risk DHL patients in our model have an OS (59%) comparable with that of routine DLBCL patients treated with R-CHOP who have high-risk R-IPI scores. Notably, a significant proportion of the high-risk patients in our model were alive at 2 years (41%), demonstrating the possibility of a favorable outcome even in high-risk DHL patients. As one might assume, patients who do not achieve CR face much poorer OS, with particularly dismal outcomes for those who have stable disease or progressive disease as first response (data not shown). In fact, the 2-year OS of patients achieving CR, but not consolidated with SCT, is >75%, suggesting that the dominant predictive factor of outcome is achieving CR with induction therapy.

No study has yet identified a regimen associated with improved outcomes for patients with DHL, though the number of patients in prior studies have been small.[12,18,25] A phase 3 trial comparing R-CHOP with DA-EPOCH-R in patients with DLBCL unselected for adverse prognostic factors completed accrual in mid-2013,[31] but it is unclear whether this study will have sufficient quantity of DHL patients to assess the role of intensive induction. Our data suggesting improvement in outcome favoring intensive therapy warrants

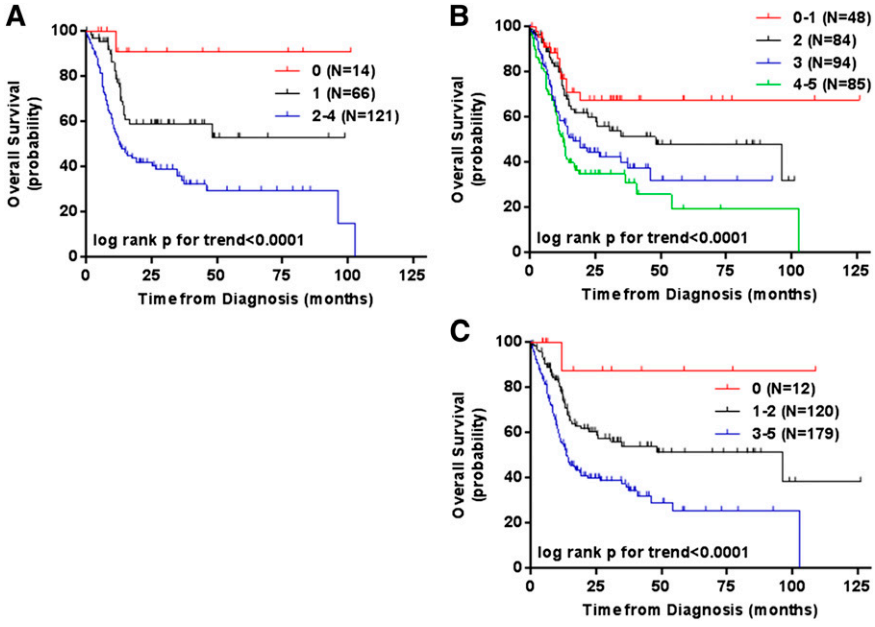


Figure 4. Overall survival by novel prognostic score, IPI, and R-IPI. Kaplan-Meier curves demonstrating overall survival (OS) by (A) a novel prognostic score among 201 patients with all data available; by (B) the original international prognostic index (IPI); and by (C) the R-IPI, for patients with DLBCL treated in the rituximab era. In the novel prognostic score, patients are assigned one point for each of the following: leukocytosis, lactate dehydrogenase >3× ULN, Ann Arbor stage 3 or 4 disease, and CNS involvement.

further investigation, though it is important to note that selection bias may have contributed to differences in outcomes with respect to retrospective data such as these.

Our MVA indicates that age, ECOG PS, and extranodal disease each lose prognostic significance for patients with DHL, whereas advanced stage and LDH retain their importance. ECOG PS and multiple extranodal sites of disease may lose their prognostic significance in our MVA because these factors commonly coexist in patients who also have advanced-stage and elevated LDH, which may have decreased their independent prognostic value in our high-risk population. Elevated LDH was a significant factor on MVA in our study only when the cutoff of $>3\times$ ULN was used. This may be because most DHL patients in our study had an elevated LDH (76%). This confirms the findings of other authors that a dichotomous division between elevated or normal LDH may not offer ideal prognostic discrimination for patients with DLBCL, compared with more refined incremental divisions.[32,33] The DPI in this study may assist in identifying patients with DHL who carry a particularly favorable prognosis. The traditional IPI identifies a similar low-risk population with an IPI score of 0.

In our study, CNS involvement and leukocytosis emerged as additional predictors of outcome for patients with DHL. The significance of leukocytosis may reflect a relatively higher frequency of leukemic-phase disease compared with conventional DLBCL.[12] We confirm a very poor prognosis for patients presenting with CNS involvement, as has been well-reported in DLBCL as a whole. Our data also suggest a possible role for the incorporation of CNS prophylaxis into the initial therapy of this disease, though this analysis is limited by selection bias given the retrospective nature of who was selected to receive CNS prophylactic therapy and who was not. Among CNS prophylaxis strategies, we cannot discern from our data whether intrathecal or systemic CNS prophylaxis may be preferable. Given the high rate of CNS involvement (in our series and others), CNS staging and incorporation of prophylactic therapy certainly seems warranted for DHL patients.

Regardless of induction regimen, patients with DHL face steep initial drops in curves of both PFS and OS, suggesting unacceptably high rates of early treatment failure and death. Our data demonstrated very poor outcomes in relapsed or refractory DHL patients despite salvage therapy. These results echo what has previously been observed in *MYC*-rearranged DLBCL patients in whom chemoimmunotherapy followed by HDT-ASCT produced inferior CR rates, PFS, and OS compared with patients without *MYC* rearrangements, irrespective of presence or absence of additional translocations.[34] This finding suggests that further escalation in chemotherapy intensity in the salvage setting is unlikely to yield significant benefit, and that the incorporation of novel agents as part of both induction and salvage therapy should be investigated.

Despite the weaknesses inherent in a retrospective analysis including nonuniform screening (late median year of diagnosis suggests that screening for DHL is more common now than even several years ago), treatments and follow-up, and missing data, our study has the strengths of including a large number of patients with an uncommon disease, drawn from multiple centers. Collectively, our data are hypothesis-generating and support a possible role for intensive induction therapy and consideration of consolidative stem cell transplant in first remission. Because the ability to discriminate individual prognoses remains imperfect, with many facing dismal outcomes, DHL represents an unmet medical need that will require incorporation of novel agents as opposed to intensification of existing ones. We also demonstrate that a subset of patients with DHL will have a favorable prognosis and can be identified using our novel prognostic index.

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Authorship

Contribution: A.M.P. and M.D.G. designed the study, collected and interpreted data, coordinated multicenter effort, and co-authored and revised the manuscript; B.J. interpreted data and performed statistical analyses; J.J.C., S.R., D.T.Y., K.A.S., J.D.W., L.X.L., S.M., C.A., N.D., C.H., J.P.T., C.H., H.S., and J.J. collected data; J.C., F.L., F.J.H., S.K.B., R.K., S.S., C.N., D.P., J.V., A.E., N.S., T.F., A.Z., D.L., A.M., N.R., S.L., C.R.F., J.B.C., K.A.B., K.S., O.P., R.C., J.M., S.S., and A.R.S. collected and interpreted data and revised the manuscript; and J.S.A. collected and interpreted data and co-authored and revised the manuscript.

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