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REVIEW

Drug therapy for double-hit lymphoma

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Abstract

Double-hit lymphoma (DHL) is a rare type of aggressive B-cell lymphoma defined as a high-grade B-cell lymphoma (HGBCL) with the presence of MYC, BCL2 and/or BCL6 rearrangements. Patients usually present with rapidly progressive and advanced stage of disease and, commonly, with extranodal involvement. Typically, patients become refractory to standard R-CHOP, and more aggressive regimens such as DA-EPOCH-R, R-hyperCVAD or CODOX-R regimens are typically needed. MYC is considered an "undruggable" mutation. Recent evidence suggests that pathogenic mechanisms associated with MYC could be potential targets. In this review, we also discuss the role of hematopoietic stem cell transplantation (HCT) and chimeric antigen receptor (CAR) T-cell therapy in DHL. We also discuss the role of potential novel agents such as BCL2 inhibitors, checkpoint inhibitors, bromodomain and extraterminal (BET) family inhibitors, Pi3K inhibitors, and others.

Keywords: double-hit lymphoma, MYC, targeted therapy.

Citation

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Introduction

Diffuse large B-cell lymphoma (DLBCL) encompasses a spectrum of pathologic and molecular subtypes with different biologic behaviors, responses in treatment, and outcomes. Now categorized as high-grade B-cell lymphoma (HGBL), the 2016 World Health Organization (WHO) classification defines double-hit lymphoma (DHL) as HGBL harboring *MYC* rearrangement occurring with either a B-cell CLL/lymphoma 2 (*BCL2*) and/or B-cell CLL/lymphoma (*BCL6*) rearrangement.[1] These are referred to as triple-hit lymphoma (THL) if all three gene rearrangements are present, and double expressor lymphoma (DEL) is DLBCL that exhibits co-expression of the respective proteins in the absence of gene rearrangement.

The *MYC* proto-oncogene on chromosome 8q24 functions in cell proliferation, differentiation, and apoptosis, and *BCL2* on chromosome 18q21 and *BCL6* on chromosome 3q27 also regulate apoptosis. *MYC* also regulates posttranscriptional events such as the modulation of non-coding RNAs such as microRNAs (specially the miR 17-92 cluster) and RNA processing (such as splicing and capping of mRNA).[2] MYC translocation or rearranged LBCL may have poorer survival outcomes with standard chemoimmunotherapy, and the synergistic effect of dysregulation of both *MYC* with *BCL2* and/or *BCL6* rearrangements promotes lymphomagenesis and increases resistance to chemotherapy.[3–5] DHL with *MYC* and *BCL6* rearrangements occur primarily in germinal center B-cell-like (GCB) DLBCL, but can also be found in activated B-cell-like (ABC) subtype; however, combined *MYC* and *BCL2* rearranged DHL occurs predominantly in GCB subtype.[6] In a study by Scott and colleagues, more than 1,200 newly diagnosed DLBCL were analyzed by cell of origin (COO) and fluorescence in situ hybridization (FISH) to detect c-*MYC*, *BCL2*, and *BCL6* rearrangements, and of the 7.9% DLBCL cases assigned to DHL/HGBL; these comprised 13% GCB signature versus 1.7% within ABC category.[6] DEL are defined by overexpression on immunohistochemistry (IHC) of both c-*MYC* and *BCL2* (>40% and >50%, respectively), are usually from the ABC subtype.[7]

Although gene expression profiling (GEP) serves as the reference standard for identification of cell of origin, it is not widely available, and IHC-based algorithms (i.e., Hans algorithm) continue to be routinely utilized.[8] Thus, biologic heterogeneity with distinct molecular subgroups within GCB and ABC still needs further characterization to subsequently translate into clinical applications.[9] The NanoString gene expression system utilizes sequence-specific probes for direct measurement of mRNA without amplification. Compared with IHC, NanoString

has the ability to perform multiplex analyses of hundreds of distinct targets while only needing a small amount of input from formalin-fixed, paraffin-embedded diagnostic tissue.[10]

Characterizing gene expression signatures within DLBCL facilitates identification of molecular subtypes based on co-occurrence of genetic alterations that may determine clinical behavior, prognostication, and future targets for treatment.[11,12] Using exome and transcriptome sequencing, array-based DNA copy-number analysis, and targeted amplicon resequencing, Schmitz and colleagues identified four prominent genetic subtypes in DLBCL: MCD with co-occurrence of MYD88 and CD79B mutations, BN2 with BCL6 fusions and NOTCH2 mutations, N1 based on NOTCH1 mutations, and EZB with EZH2 mutations and BCL2 translocations.[12] Each subtype differs in clinical phenotype and outcomes with chemoimmunotherapy, with more favorable responses and survival in the BN2 and EZB subtypes while MCD and N1 had inferior outcomes.

Ennishi and colleagues also developed a double-hit signature (DHITsig) that identified a distinct subgroup within DLBCL with inferior outcomes irrespective of DHL/THL or HGBL status.[13] Further utilizing DHITsig, Hilton and colleagues evaluated 20 DHITsig-positive GCB-DLBCL cases with whole genome sequencing and identified DHITsig-positive DLBCL not rearranged and cryptic to break-apart FISH, adding to the importance of refining molecular characterization.[14] Rosenwald and colleagues analyzed the role of MYC rearrangements in a large cohort of patients with the goal of evaluating the role of the non-immunoglobulin (IG) partner in the outcomes of DLBCL. Overall, DLBCL patients with single-hit MYC rearrangement with an IG or non-IG partner had the same prognostic effect as DHL/THL with a non-IG partner (as opposed to DHL/THL with IG partner as translocations that had a very poor prognosis in this cohort). This effect was exclusively seen within the first 2 years after diagnosis.[4]

Although DHL only represents around 10% of newly diagnosed HGBL,[1,2] these patients more commonly present with advanced stage III or IV disease with high-risk international prognostic index (IPI) score, and they are more likely to have extranodal and/or central nervous system (CNS) involvement.[15,16] DHL/THL has a worse prognosis with inferior outcomes when treated with R-CHOP without high-dose chemotherapy consolidation, especially when patients do not achieve a complete response (CR). The utilization of intensive chemotherapy regimens has helped improve responses, but robust data on improvement in overall survival (OS) are lacking.[17–20]. Ongoing research strives to optimize frontline treatment of DHL as well as evaluate new treatment strategies in the relapsed/refractory (R/R) setting, and the growth of gene expression profiling with associated targeted therapies provides new potential therapeutic strategies.[12]

Herein, we review the current standard of care for management of DHL with chemoimmunotherapy and the role of hematopoietic stem cell transplant (HSCT). We also review the potential role of chimeric antigen receptor T-cell (CART) therapy as well as evidence for other evolving treatments that may play a future role in the treatment of DHL. Investigational therapies include agents targeting bromodomain containing 4 (BRD4), cyclin-dependent kinase (CDK), histone deacetylase (HDAC), phosphoinositide 3-kinase (PI3K), aurora kinase, EZH2, BCL2 family, and checkpoint inhibition.

Chemoimmunotherapy

R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) remains the standard of care for DLBCL. However, DHL, DEL, and *MYC* rearranged DLBCL/HGBL have inferior progression-free survival (PFS) and OS when treated with R-CHOP with 5-year PFS and OS approximately 20–30%.[19,21–23] Based on these historical outcomes, currently many centers consider higher-intensity chemotherapy regimens in DHL, such as dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab), R-HyperCVAD/MA (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate, cytarabine), and R-CODOX-M/IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine).

A prospective, single-arm phase II study of 53 patients with untreated aggressive B-cell lymphoma with *MYC* rearrangement received six cycles of DA-EPOCH-R with CNS prophylaxis with a total of eight doses of intrathecal methotrexate.[24] Twenty-four of 53 (45%) patients had confirmed DHL/THL, and the 48-month event-free survival (EFS) and OS values were 73.4% and 82%, respectively, indicating improved outcomes over R-CHOP based on historical controls. Dose adjustments were carried out based on count nadir with grade 4 toxicities primarily related to neutropenia and thrombocytopenia, and three treatment-related deaths were related to infections.[24]

Retrospective data also showed improved response rates and PFS with R-HyperCVAD/MA and R-CODOX-M/IVAC as well as DA-EPOCH-R compared to R-CHOP. The highest rates of CR were seen with DA-EPOCH-R in the 50–60% range, compared to CR rates of 32–36% achieved with R-HyperCVAD/MA and R-CODOX-M/IVAC[25-27]. The largest retrospective, multi-institutional cohort of 311 treatment-naïve DHL patients showed a median PFS of 7.8 months when treated with R-CHOP compared with 21.6 months for those treated with more intensive chemotherapies.[25] CR was associated with improved outcomes by multivariant modeling, and deeper responses were achieved with intense therapies. However, significant improvement in OS has not been observed across all retrospective data sets.[25–27]

The recent large phase III Intergroup Trial Alliance/CALGB 50303 prospective study of 491 eligible patients with newly diagnosed DLBCL compared frontline DA-EPOCH-R with R-CHOP.[28] Among all patients, there was no significant difference in survival with 2-year PFS 78.9% for DA-EPOCH-R and 75.5% for R-CHOP, and 2-year OS was 86.5% for DA-EPOCH-R and 85.7% for R-CHOP. There were 270/491 (55.0%) patients in the trial who were assessed for double expressor status, and 42 patients were classified as

DEL. *MYC* rearrangement data were available for 249/491 (50.7%) patients, and 13 patients were found to be *MYC* rearranged with 3 of the 13 patients being further classified as DHL. There was no significant difference in PFS or OS between the two regimens for the 42 DEL patients, but the preplanned subgroup analysis based on FISH classification has not yet been reported.[28]

Due to the lack of appropriate prospective data, and based on several retrospective series including a systematic review and meta-analysis by Howlett and colleagues, DA-EPOCH-R is currently often preferred in clinical practice due to better risk–benefit profile.[29] R-HyperCVAD/MA and R-CODOX-M/IVAC typically have greater toxicity and are poorly tolerated in older patients[30] (Table 1).

Patients with DHL have a higher risk of extranodal involvement including CNS invasion, and the CNS-IPI score has been validated to assess risk of CNS disease in DLBCL to warrant further CNS diagnostic testing and prophylaxis.[31] However, HGBL with c-*MYC*, *BCL2,* and/or *BCL6* rearrangements were not evaluated as independent risk factors in the CNS-IPI validation cohorts. Due to significant CNS involvement at diagnosis (7–10%) with associated dismal prognosis, CNS prophylaxis is recommended for all DHL/THL patients regardless of the CNS-IPI score.[25,26] CNS prophylaxis strategies vary across prior clinical trials, but most commonly incorporate 4–8 doses of intrathecal methotrexate and/or cytarabine or systemic methotrexate during the course of chemotherapy.[32] As seen in different aggressive lymphomas, outcomes in patients presenting with CNS involvement are

Table 1. Chemoimmunotherapy studies with DHL.

Authors and study type	Number of patients included	Treatment(s) analyzed	Progression-/relapse-/event-free survival (months)	Overall survival (months)
Savage KJ et al. Blood 2009 Retrospective	12 *MYC*+ (8 BCL2+ on IHC) 123 *MYC*–	R-CHOP in *MYC*+ *vs.* *MYC*– DLBCL	5-year PFS: 66% *MYC*– *vs.* 31% *MYC*+ (p=0.006)	5-year OS: 72% MYC– *vs.* 33% MYC+ (p=0.016)
Johnson NA et al. JCO 2012 Retrospective	14 DHL 55 DEL 236 other DLBCL	R-CHOP in *de novo* DLBCL	5-year PFS: DHL: 18% DEL: 32% Non-DHL/DEL DLBCL: 65%	5-year OS: DHL: 27% (p<0.001) DEL: 36% (p=0.014) Non-DHL/DEL DLBCL: 71%
Akyurek N et al. Cancer 2012 Retrospective	7 DHL/THL 232 other DLBCL	R-CHOP in *de novo* DLBCL	Median survival DHL/THL: 9 months (p=0.003)	DHL/THL: 2-year OS 14% (p<0.001)
Horn H et al. Blood 2013 Retrospective	29 DHL/THL 321 other DLBCL with measurable *BCL2/BCL6/MYC*	CHOP-14 +/– rituximab in de novo DLBCL on RICOVER study	3-year EFS R-CHOP DHL group: 38.1% for MYC+/BCL2+ (CI: 0.0–77.1) 50.0% for MYC+/BCL6+ (CI: 1.0–99.0)	3-year OS R-CHOP DHL group: 35.7% for MYC+/BCL2+ (CI: .0–74.5) 75.0% for MYC+/BCL6+ (CI: 32.5–100.0)
Petrich AM et al. Blood 2014 Retrospective	311 total patients 286 DHL 25 THL	R-Hyper-CVAD: 65 patients DA-EPOCH-R: 64 patients R-CODOX-M/IVAC: 42 patients R-CHOP: 100 patients R-ICE: 9 patients Other regimens: 31 patients	Median PFS: Intensive regimen: 21.6 months R-CHOP: 7.8 months (p=0.001) All patients: 10.9 months 2-year PFS all patients: 40%	Median OS all patients: 21.9 months Median OS NR if CR to frontline therapy; no difference with consolidation auto/allo SCT 2-year OS all patients: 49%
Oki Y et al. BJH 2014 Retrospective	129 DHL	R-CHOP: 57 patients R-EPOCH: 28 patients R-HyperCVAD/MA: 34 patients Other regimen: 10 patients	2-year & 3-year EFS: R-CHOP: 25% & 20% R-EPOCH: 67% & 67% R-HyperCVAD/MA: 32% & 32% Other: < 10% & < 10% All: 33% & 29%	2-year & 3-year OS: R-CHOP: 41% & 35% R-EPOCH: 76% & 76% R-HyperCVAD/MA: 44% & 40% Other: <12% & <12% All: 44% & 38%

(*Continued*)

Table 1. (*Continued*)

Authors and study type	Number of patients included	Treatment(s) analyzed	Progression-/relapse-/event-free survival (months)	Overall survival (months)
Sun H et al. Clin Lym Leuk 2015 Retrospective	32 DHL (16 received transplant)	CODOX-M/IVAC-R +/– consolidative SCT	2-year PFS: All patients: 41% Transplant patients: 60%	2-year OS: All patients: 53% Transplant patients: 82%
Howlett C et al. BJH 2015 Retrospective systematic review and meta-analysis	11 studies 394 patients	R-CHOP: 180 patients DA-EPOCH-R: 91 patients DI (R-HyperCVAD/rituximab, methotrexate, cytarabine (R-M/C), R-CODOX-M/R-IVAC): 123 patients	Median PFS: R-CHOP: 12.1 months DA-EPOCH-R: 22.2 months DI: 18.9 months RR DA-EPOCH-R: 34% (p=0.032)	Median OS: R-CHOP: 21.4 months DA-EPOCH-R: 31.4 months DI: 25.2 months No significant difference OS
Landsburg DJ et al. JCO 2017 Retrospective	159 DHL 62 AutoSCT in CR1	R-CHOP: 35 patients DA-EPOCH-R: 81 patients R-HyperCVAD: 32 patients R-CODOX-M/IVAC: 11 patients	3-year RFS (p=0.003): R-CHOP: 56% DA-EPOCH-R: 88% R-HyperCVAD: 87% R-CODOX-M/IVAC: 91%	3-year OS (p=0.36): R-CHOP: 77% DA-EPOCH-R: 87% R-HyperCVAD: 90% R-CODOX-M/IVAC: 100%
Dunleavy K et al. Lancet Haematology 2018 Prospective single-arm phase II study	24 DHL/THL 19 MYC-rearranged 10 HGBL NOS	DA-EPOCH-R for 6 cycles CNS prophylaxis: IT MTX Days 1 & 5 of cycles 3–6	48-month EFS: DHL: 73.4% (95% CI: 50.1–87.1) All Patients: 71.0% (95% CI: 56.5–81.4)	48-month OS: DHL: 82.0% (95% CI: 58.8–92.8) All patients: 76.7% (95% CI: 62.6–86.1)
Bartlett NL et al. JCO 2019 Phase III Intergroup Trial Alliance/CALGB 50303	491 DLBCL (42 DEL, 13 MYC rearranged, 3 confirmed DHL)	R-CHOP *vs.* DA-EPOCH-R as frontline therapy for DLBCL R-CHOP: 250 patients DA-EPOCH-R: 241 patients	DA-EPOCH-R PFS: HR 0.93 (95% CI: 0.68–1.27, p=0.65) R-CHOP: 2-year PFS: 75.5% 5-year PFS: 66.0% DA-EPOCH-R: 2-year PFS: 78.9% 5-year PFS: 68.0% DEL PFS: HR 1.75 (95% CI: 1.03–2.98, p=0.037)	DA-EPOCH-R OS: HR 1.09 (95% CI: 0.75–1.59, p=0.64) 2-year OS: R-CHOP: 85.7% DA-EPOCH-R: 86.5% 5-year OS: R-CHOP: 78.5% DA-EPOCH-R: 77.5%

CI, confidence interval; DEL, double expressor lymphoma; DHL, double hit lymphoma; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; SCT, stem cell transplant; THL, triple hit lymphoma.

particularly poor, and inferior outcomes have been observed in patients who did not receive CNS-directed prophylaxis.[25,26]

With R/R DHL, there is currently no standard of care for optimal salvage second-line chemotherapy treatments and beyond. Traditional DLBCL management with salvage regimens such as R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) or R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) followed by autologous stem cell transplantation (autoSCT) result in inferior PFS and OS for DHL compared with DLBCL without *MYC* rearrangements.[33,34] This emphasizes the need for further research into novel treatments to expand options available as standard care.

HSCT

With intensive chemoimmunotherapy regimens such as DA-EPOCH-R becoming the standard of care for DHL, there have been attempts to further intensify treatment with

consolidative autoSCT. If a patient does not receive intensive chemoimmunotherapy frontline, autoSCT as consolidation after R-CHOP may help improve relapse-free survival (RFS) and OS compared with R-CHOP alone.[35] Patients receiving R-CHOP without autoSCT in the first CR (CR1) had 3-year RFS of 51% and OS of 75%, but patients who received R-CHOP frontline with autoSCT in CR1 had 3-year RFS 75% with OS 83%, indicating improved outcomes. However, in patients who received a frontline intensive regimen (such as DA-EPOCH or R-HyperCVAD) with subsequent CR1, consolidative autoSCT was not associated with improved survival outcomes.[25,26,35,36].

High-dose chemotherapy with autoSCT remains a standard of care for R/R DLBCL achieving CR after salvage chemotherapy. However, in the setting of DEL/DHL the outcomes are particularly poor. For R/R DEL and DHL, retrospective data of 117 patients with chemotherapy-sensitive R/R DLBCL reported inferior PFS and OS with autoSCT within the DEL/DHL patients.[37] For 47 DEL patients, there was a 4-year PFS of 48% and 4-year OS of 56%, and the non-DEL patients had 4-year PFS and OS of 59% and 67%, respectively. The 12 DHL patients had a 4-year PFS of 28% and 4-year OS of 25%, whereas the non-DHL patients had 4-year PFS and OS of 57% and 61%, respectively.[37] Newer treatment modalities for R/R DEL/DHL may supplant the role of autologous HSCT.

Limited data on outcomes of allogeneic stem cell transplantation (alloSCT) in DHL and efficacy of graft-versus-lymphoma for R/R DHL/DEL are available.[38] Herrera and colleagues retrospectively studied outcomes after alloSCT in 78 patients with R/R aggressive B-cell non-Hodgkin lymphoma, and 37/78 (47%) had DEL, whereas 10/78 (13%) had DHL.[39] There was no significant difference in PFS or OS after alloSCT irrespective of DEL and DHL status, indicating its potential role for producing durable remissions. Although alloSCT may potentially provide durable remissions for those with poor prognosis in R/R DEL/DHL, this must be carefully weighed with the risks of transplant-related mortality and long-term complications[40,41] (Table 2).

CART therapy

CART cell therapy has revolutionized the treatment of R/R DLBCL, and this has significantly changed the previously very poor prognosis in the chemoresistant or post-HDT-autoSCT relapse setting. Chimeric antigen receptors (CARs) consist of fusion proteins with antigen-recognition and T-cell signaling domains, and patients' T-cells with engineered anti-CD19 CARs recognize lymphoma B-cells expressing CD19 for destruction with enhanced responses utilizing costimulatory domains.[42] CART has produced dramatic response rates and durable remissions for R/R DLBCL.[43,44]

Axicabtagene ciloleucel (Yescarta®) developed by Kite Pharma consists of a CD3z-CD28 CART construct, and tisagenlecleucel (Kymriah®) produced by Novartis is an anti-CD19 CART that uses 4-1BB as a costimulatory domain.[45,46] The phase I–II ZUMA-1 trial with axicabtagene ciloleucel found an objective response rate of 83% with 58% of patients achieving CR, 25% with partial

Table 2. Studies of stem cell transplant in DHL.

Authors and study type	Patients included	Progression-/relapse-/event-free survival (months)	Overall survival (months)
Peniket AJ et al. BMT 2003 Retrospective	255 alloSCT for high-grade NHL	Median PFS: 7.1 months 4-year PFS: 39.3%	Median OS: 1 year 4-year OS: 41.2% 4-year procedure-related mortality: 33.0%
Petrich AM et al. Blood 2014 Retrospective	311 total patients: 286 DHL, 25 THL	Not reported for transplant patients: 83 total SCT patients including 39 autoSCT and 14 alloSCT in CR1	Median OS: Observation with CR1: 103 months Consolidation SCT (any type): not reached (p=0.14) Auto- or allo-SCT in CR1: not reached (p=0.302)
Oki Y et al. BJH 2014 Retrospective	129 DHL: 71 achieved CR1 23 SCT in CR1	EFS all stages achieving CR, frontline SCT: HR 0.53 (95% CI: 0.21–1.31, p=0.170) EFS advanced stage achieving CR, frontline SCT: HR 0.42 (95% CI: 0.17–1.05, p=0.065)	All stages achieving CR, frontline SCT: HR 0.74 (95% CI: 0.27–2.04, p=0.566) Advanced stage achieving CR, frontline SCT: HR 0.58 (95% CI: 0.21–1.60, p=0.292)

(*Continued*)

Table 2. (*Continued*)

Authors and study type	Patients included	Progression-/relapse-/event-free survival (months)	Overall survival (months)
Landsburg DJ et al. JCO 2017 Retrospective	159 DHL: 62 AutoSCT in CR1 27 R-CHOP/Non-AutoSCT 8 R-CHOP/AutoSCT 70 Intensive/Non-AutoSCT 54 Intensive/AutoSCT	3-year RFS: All patients: 80% AutoSCT in CR1: 75% Non-AutoSCT: 89% R-CHOP/Non-AutoSCT: 51% R-CHOP/AutoSCT in CR1: 75% Intensive Regimen/Non-AutoSCT CR1: 86% (p=0.002, compared with R-CHOP) Intensive Regimen/AutoSCT CR1: 91%	3-year OS (No significant difference): All patients: 87% AutoSCT in CR1: 85% Non-AutoSCT: 91% R-CHOP/non-autoSCT: 75% R-CHOP/autoSCT in CR1: 83% Intensive regimen/non-autoSCT CR1: 89% Intensive regimen/autoSCT CR1: 92%
Herrera AF et al. JCO 2017 Retrospective	117 DLBCL s/p autoSCT: 52 DEL 12 DHL	4-year PFS: Non-DEL/DHL: 60% (95% CI: 46–72) DEL: 48% (95% CI: 34–61) DHL: 28% (95% CI: 6–57, p=0.013)	4-year OS: Non-DEL/DHL: 70% (95% CI: 55–80) DEL: 56% (95% CI: 40–69) DHL: 25% (95% CI: 5–54, p<0.001)
Chen AI et al. Leuk Lymph 2018 Retrospective	36 DHL treated with DA-EPOCH-R 17 received autoSCT	2-year PFS: 69% (95% CI: 54–84) 2-year PFS autoSCT: 94% (95% CI: 83–100) 2-year PFS observation: 79% (95% CI: 52–100) (p=0.59)	2-year OS: 71% (95% CI: 56–86) 2-year OS autoSCT: 94% (95% CI: 83–100) 2-year PFS observation: 79% (95% CI: 52–100) (p=0.59)
Herrera AF et al. Biol BMT 2018 Retrospective	78 total HGBL: 31 DEL 10 DHL	4-year PFS: DHL: 40% (p=0.62) Non-DHL: 34% DEL: 30% (p=0.24) Non-DEL: 39%	4-year OS: DHL: 50% (p=0.46) Non-DHL: 38% DEL: 31% (p=0.46) Non-DEL: 49%
Salhotra A et al. Biol BMT 2019 Retrospective	22 patients with lymphoma s/p alloSCT: 10 DLBCL	2-year EFS: 58.3% (95% CI: 35–75.8) 2-year cumulative incidence of relapse: 31.8% (95% CI: 13.6–51.8)	2-year OS: 45.5% (95% CI: 24.4–64.3) 2-year non-relapse mortality: 27.7% (95% CI: 8.0–42.0)

alloSCT, allogeneic stem cell transplant; autoSCT, autologous stem cell transplant; CI, confidence interval; CR, complete remission; CR1, first complete remission; DEL, double expressor lymphoma; DHL, double hit lymphoma; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; SCT, stem cell transplant.

response, and 10% with stable disease.[47] With a median follow-up of 27.1 months, the median duration of response (mDOR) on ZUMA-1 was 11.1 months for all patients (95% confidence interval [CI] 4.2-not estimable) and not reached for patients in CR (95% CI 12.9-not estimable). Median OS was not reached (95% CI 12.8-not estimated) with PFS 5.9 months (95% CI 3.3–15.0 months), and 39% of patients had an ongoing response. By investigator assessment, 33 patients had DE/HGBL with seven patients with confirmed DHL/THL or HGBL that achieved 90% objective responses and 33% ongoing CRs at last follow up.[47]

The JULIET trial with tisagenlecleucel observed a best overall response rate of 52% (95% CI: 41–62) with 40% achieving CR whereas 12% had partial responses (PR), and 12-month RFS was 65%.[46] Of the 19 patients with confirmed DHL/THL on the JULIET trial, there was a response rate of 50% and CR rate of 25%. The TRANSCEND-NHL-001 study is currently testing lisocabtagene maraleucel (JCAR017 or liso-cel) construct with 4-1BB costimulatory molecule with a predefined 1:1 CD4:CD8 ratio, and initial phase I data report a best overall response rate of 75–84% in all DLBCL patients and 81% among the 16 patients

Table 3. CART studies that included DHL.

Authors and study type	Patient population	Clinical efficacy	Response durations
Abramson JS et al. JCO 2018 phase 1 TRANSCEND NHL 001 trial	91 patients received lisocabtagene maraleucel (JCAR017) (81 evaluable for efficacy)	ORR: 74% in FULL dataset, 80% in CORE dataset CR: 52% in FULL, 55% in CORE CORE dataset, dose-level 2: ORR 50%, CR 50% CORE dataset, dose-level 1: ORR 40%, CR 30%	Not reported
Locke FL et al. Lancet Oncol 2019 Single-arm, phase I/II ZUMA-1 trial	101 assessable patients received axicabtagene ciloleucel: 30 DEL 7 HGBL (1 THL, 4 DHL, 2 HGBL NOS)	All patients: Objective Response: 83% CR: 58% PR: 25% SD: 10% PD: 5% DEL/HGBL patients: Objective Response: 91% CR: 70%	All patients: Median time to response: 1 month Median duration of response: 11.1 months Median duration of response if CR: Not Reached Median PFS: 5.9 months (95% CI: 3.3–15.0) 24-month PFS: 72.0% if CR at 3 months, 75.0% if PR at 3 months, 22.2% if SD at 3 months
Schuster SJ et al. NEJM 2019 Single-group phase II JULIET trial	93 patients with relapsed/refractory DLBCL received tisagenlecleucel	ORR: 52% (95% CI: 41–62) CR: 40% PR: 12%	12-month RFS: 65% (79% among patients with CR)

CI, confidence interval; CR, complete response; DHL, double hit lymphoma; DLBCL, diffuse large B-cell lymphoma; HGBL NOS, high-grade B-cell lymphoma not otherwise specified; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RFS, relapse-free survival; SD, stable disease; THL, triple hit lymphoma.

with DHL/THL.[48,49] The DHL/THL patients also had a 3-month CR rate of 60%, also within the range of all DLBCL patients under study (Table 3).

The efficacy of CART therapy in refractory DLBCL was also evaluated outside clinical trials in an effort of the US CART Consortium that included nearly 300 patients treated with axi-cel after its FDA approval in October 2017.[50] The objective responses and CR rates were 81% and 57%, respectively, and similar to the ZUMA-1 findings. This data set included 62 patients with DHL/THL, and although the report did not include overall efficacy rates, the multivariate analysis showed that DHL/THL status was not predictive of the lack of response.

Although CART therapy has changed the landscape of DLBCL treatment, relapses do occur. Some of the strategies include targeting the tumor microenvironment (TME). The checkpoint molecules PD-1 and PD-L1 are present and upregulated in CART cells and TME, especially after infusion.[51] A clinical trial evaluated the efficacy of pembrolizumab 200 mg every 3 weeks until disease progression in R/R DLBCL post-tisagenlecleucel infusion. The study included 12 patients and showed an ORR of 27% (one patient achieved CR). Re-expansion of CART cells were noted after the first infusion of pembrolizumab. The ZUMA-6 study examined the efficacy of axicabtagene ciloleucel in combination with atezolizumab (PD-L1 inhibitor) at doses of 1200 mg every 3 weeks at different starting points (cohorts). The phase 1 portion was completed and showed an ORR and CR rates of 90% and 60%, respectively. CART cell expansion was twice higher than that in ZUMA-1-treated patients. Of interest, grade 3 NT was higher (50%) than that reported in the ZUMA-1 trial.

Further enhancement of CART involves optimizing the expansion and persistence of CART. Preclinical models have shown potential synergistic immunomodulatory effects and increased activity of CART targeting CD19 with combining agents such as lenalidomide, Bcl-2 family apoptosis inhibitors, and ibrutinib.[52–54] Potential mechanisms for enhancing antitumor function of CART include stronger signaling via CAR, increased interferon gamma production, increasing tumor cell apoptosis, and other possible immune-mediated mechanisms of deepening or augmenting the response of CART.

Potential novel targets

Despite being one of the most characterized oncogenes, c-MYC has been considered the "undruggable" target, and efforts to

successfully target MYC have been disappointing. Thus, many the efforts carried out in MYC-related lymphomas have focused on targeting post-transcriptional or translational mechanism that regulates MYC expression and function.

Bromodomain-containing 4 (BRD4) inhibitors

BRD4 is a key component of the bromodomain and extra-terminal (BET) family and it also a key regulator of the transcriptional process of MYC. BRD4 specifically binds acetylated histones among those the transcription elongation factor b (P-TEFb) that enhances transcriptional functions. BET inhibitors compete with BRD4 binding sites and displace promoters/enhancers of the MYC oncogene. Preclinical data showed that the BET inhibitor, birabresib (OTX015), showed antitumor activity especially in ABC subtype DLBCL cell lines as single agent and in combination with other agents such as rituximab, ibrutinib, everolimus, and vorinostat.[55,56] A phase I clinical trial included 33 patients with lymphoma. Objective responses were seen in 40% ABC-DLBCL (10), 17% GCB-DLBCL (17), and 20% of MYC+ DLBCL (5).[57] There are ongoing clinical trials specifically in MYC-altered DLBCL in combination with venetoclax that are currently enrolling (NCT03255096).

CDK7 and CDK9

MYC deregulation and enhanced transcription are related to super-enhancers (SEs) that include transcription factors and chromatin regulators such as CDK7 and CDK9. As opposed to other CDKs (that regulates cell cycle transition), CDK7 and CDK9 are tightly related to transcription initiation and elongation. Current ongoing trials are not only focused in lymphomas but in myeloid malignancies and solid tumors.[58] Recent evidence shows that voruciclib (a CDK9 inhibitor) seems to synergize with BCL2 inhibitors through MCL-1 inhibition (which is a known resistance mechanism for BCL-2 inhibitors in lymphomas).[59] There is currently a clinical trial with voruciclib that includes patients with DLBCL (NCT03547115).

Dual histone deacetylases (HDAC) and PI3K

HDACs are critical in maintaining acetylation of histones that are key in gene expression and DNA transcription. Their role in cancer and specifically in lymphomas is very well established. The PI3Ks are also a very well-known B-cell lymphoma pathway. HDAC has been shown to affect MYC expression and BCL2 regulation.[60] PI3K is known to decrease MYC stability by dysregulating the post-transcription phase of MYC-dependent proteins.[61] In DLBCL cell lines and mouse models, HDACs and PI3K inhibition have been shown to have a synergistic antitumor effect through MYC-dependent transcriptional pathways.[62] There are currently several HDAC and PI3K inhibitors that have been approved by the FDA for the treatment of lymphomas and chronic lymphocytic leukemia.

A phase I trial studied the safety and tolerability of fimepinostat, a dual HDAC/PI3K inhibitor (formerly CUDC-907), and included 40 patients with lymphoma and four patients with multiple myeloma. Among lymphoma patients there were 12 DLBCL patients. Remarkably, five of nine evaluable DLBCL patients (five with transformed follicular lymphoma) had an objective response (PR + CR).[63] The expanded Phase I trial with this agent included 14 patients with relapsed MYC-altered DLBCL with an objective response of 64% and mDOR of 13.6 months.[64] A pooled analysis of the phase I and II portions included 60 patients with MYC-altered DLBCL and showed an objective response in 14 patients (23%) with an mDOR of 13.6 months.[65] Fimepinostat is being currently tested in a phase I clinical trial in combination with venetoclax (NCT01742988).

Aurora kinase Inhibitors

The Aurora kinase family are key regulators of mitosis and have several subcomponents. Aurora kinase A (AURKA) is associated with tumor development mediated by interactions between TP53 and MYC. Overexpression of AURKA has been associated with increased malignant transformation of normal cells.[66] Alisertib (MLN8237) is an oral Aurora kinase A inhibitor that was tested in a Phase 1 clinical trial in combination with rituximab (MR) and rituximab plus vincristine (MRV) for refractory aggressive B-cell lymphomas and included 45 patients (37 evaluable patients). The objective response was 38% (MR 25% and MRV 44%) with a mDOR of 10.6 months. Of the 10 responding patients with available tissue for correlative studies, none had MYC overexpression.[67]

EZH2 inhibitors

EZH2 mutations occur in approximately 20% of DLBCL-GCB subtype, and subsequent aberrations in histone methylation can silence tumor suppressor genes and promote lymphomagenesis.[11] Tazemetostat is a first-in-class selective inhibitor of *EZH2*, and phase I data from 21 patients with B-cell non-Hodgkin lymphomas yielded objective responses in 8 of them (38%).[68] An interim update of the phase II study with tazemetostat 800 mg twice daily found overall response rates of 17% in those with and without EZH2 mutations and 9% when in combination with prednisolone.[69] A phase Ib LYSA study of tazemetostat in combination with R-CHOP also found a recommended phase II dose of 800 mg twice daily, and a phase II trial is ongoing.[70]

BCL2 inhibitors

BCL2 plays a role in regulating the apoptotic pathway with overexpression leading to resistance to cell death, and BCL2 translocations are present in 15 to 30% of DLBCL, whereas BCL2 amplification occurs in 8 to 30% of patients.[71] Venetoclax is a highly selective BCL2 inhibitor commonly used in other disease types including chronic lymphocytic leukemia and

acute myeloid leukemia that may also offer potential activity in DLBCL.[72] The phase Ib CAVALLI trial evaluated venetoclax in dose escalation in combination with R-CHOP or obinutuzumab with CHOP (G-CHOP). A recommended phase II dose of venetoclax 800 mg days 4 to 10 of cycle 1 and days 1 to 10 of cycles 2 through 8 was determined. Overall response rates seen were 87.5% in R-/G-CHOP with venetoclax, and CR was achieved in 79.2% who received R-CHOP and 78.1% with G-CHOP in combination with venetoclax.[71]

Checkpoint inhibitors

Immune checkpoint blockade targeting programmed cell death-1 receptor (PD-1) or its ligand (PD-L1) as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) dramatically improves outcomes and survival in different diseases such as malignant melanoma and lung cancers. Pembrolizumab is currently FDA approved for R/R primary mediastinal large B-cell lymphoma (PMBCL) based on KEYNOTE-170/-013, but PMBCL typically has higher expression of PD-L1 compared with DLBCL.[73,74] The clinical efficacy of PD-1 inhibition in DLBCL as a single agent is very low (ORR and CR rates at 10 and 3%, respectively), likely due to low PD-L1 expression (especially in DHL/THL) and/or low frequency of 9p24.1 genetic alterations.[75,76]

Conclusions

DHL remains an unmet need and is still considered a difficult-to-treat lymphoma. While significant progress has been made in understanding the best frontline regimens, DHL is still considered a poor prognosis disease. There is promising activity with CART cell therapy, but the proper timing and post-remission approach is yet to be determined. Targeted approaches focusing on MYC-related pathways (BRD4, CKD6 and 9, HDAC, etc.) are needed.

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