Real-World Outcomes in Patients with Relapsed or Refractory (r/r) Aggressive Large B-cell Lymphoma (LBCL) Treated with Chemo-Immunotherapy

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BACKGROUND

- World Health Organization Classification of Haematolymphoid Tumours recognizes 18 specific entities as Large B-cell Lymphoma (LBCL), with diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) being the most common.[1]
- The treatment landscape for LBCL has evolved dramatically in recent years with the introduction of chimeric antigen receptor (CAR) T-cell therapy and novel agents.[2-5]
- However, chemo-immunotherapy (CIT) remains a common standard of care for patients with r/r disease after ≥2 previous lines of therapy (LOTs).[6,7]
- Understanding real-world outcomes in the modern era is important to measure the impact of recent advances in the treatment landscape.

OBJECTIVE

To characterize real-world clinical outcomes of LBCL patients who received CIT in the third or later line of therapy (3L+).

METHODS

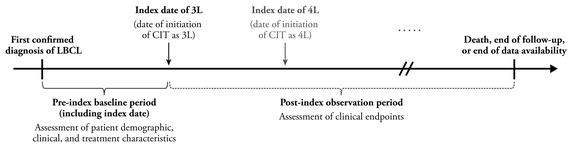
Data source

- Data from the Lymphoma Epidemiology of Outcomes (LEO) Consortium of Real-World Evidence (CReWE) cohort, a multi-site observational cohort of patients with r/r aggressive NHL (aNHL) who were diagnosed on or after 1/1/2010 and received treatment from 1/1/2015–2/15/2023, were retrospectively analyzed in this study.

Study design (Figure 1)

- The index date was the date of initiation of the first treatment in a new LOT, starting from 3L+.
  - Definition of a LOT: the LOT closest to the diagnosis date was 1L; any subsequent regimen was considered a new LOT (2L, 3L, etc.).
    - If multiple regimens/LOTs were eligible, one was randomly chosen as the index regimen/LOT.
- The baseline period was defined as the time from the first confirmed disease diagnosis up to and including the index date.
- The observation period for evaluating clinical endpoints spanned from the index date to the earliest of death, end of continuous enrollment, or end of data availability.
- CIT regimens included salvage/palliative chemotherapy, lenalidomide, rituximab, or obinutuzumab, used alone or in combination.

Figure 1. Study design scheme



Patient selection

- **Inclusion criteria**
  - Adult patients (≥18 years of age)
  - CD20+ mature B-cell neoplasm with DLBCL, primary mediastinal BCL (PMBCL), Grade 3b follicular lymphoma (FL), or high-grade BCL (HGBCL)
  - r/r disease, previously treated with ≥2 LOTs including ≥1 anti-CD20 antibody-containing therapy
  - Treated with CIT therapy as the LOT of interest
  - Previously failed or ineligible for autologous stem cell transplantation (ASCT)
  - Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0–2
  - Documented positron emission tomography (PET)-positive or PET-computed tomography (PET-CT)-positive disease at or immediately preceding the initiation of the LOT of interest
- **Exclusion criteria**
  - Primary central nervous system (CNS) lymphoma or lymphoma with CNS involvement
  - Known past or current malignancy of any type other than inclusion diagnosis or HIV infection

METHODS (CONT)

Outcomes

- Real-world **overall response rate (ORR)**: Proportion of patients with complete response (CR) or partial response (PR) as the best response for a given LOT
- Real-world **complete response (CR)**: Proportion of patients with CR as the best response for a given LOT
- Real-world **duration of response (DOR)**: Time from first documented CR or PR (as the best response) to the earliest of progressive disease (PD) or death (from any cause)
- Real-world **duration of complete response (DOCR)**: Time from first documentation of CR (as the best response) to the earliest of PD or death (from any cause)
- Real-world **progression-free survival (PFS)**: Time from initiation of a given LOT to the earliest of first documented PD or death (from any cause)
- **Overall survival (OS):** Time from initiation of an index LOT to death (from any cause)

Statistical analysis

- Descriptive statistics included mean (±standard deviation [SD]) and median for continuous variables and frequency (proportion) for categorical variables.
- Time-to-event endpoints (DOR, DOCR, PFS, OS) for patients with 3L+ were described using Kaplan-Meier curves. The median time-to-event and corresponding 95% confidence interval were reported for each endpoint.
- Outcomes were also characterized in two subgroups of patients: those with prior CAR T-cell therapy and those with DLBCL.

Patient disposition: 3L+ CIT-treated cohort

CIT-treated cohort (2/15/2023 data cut)

Data from LEO CReWE DLBCL database assessed for study eligibility
N=2,520

Patients with completed clinician review and had an initial lymphoma diagnosis date on or after 1/1/2010
N=1,557 (61.8%)

r/r disease and previously treated with ≥2 LOTs
N=947 (60.8%)[1]

CD20+ LBCL diagnosis (i.e., de novo DLBCL, DLBCL transformed from all indolent subtypes, grade 3b FL, PMBCL, HGBCL)
N=909 (96.0%)

Absence of CNS involvement before index date[2]
N=768 (84.5%)

3L+ CIT-treated and previously treated with ≥2 lines of systemic antineoplastic therapy including ≥1 anti-CD20 monoclonal antibody-containing therapy
N=333 (43.4%)

Failed previous ASCT, or ineligible for ASCT due to age, ECOG-PS, comorbidities, and/or insufficient response to previous treatment
N=333 (100.0%)

Documented PET- or CT-positive disease at or immediately preceding the initiation of the LOT of interest
N=299 (89.8%)

ECOG-PS score of 0–2
N=240 (80.3%)

Age ≥18 years at index
N=240 (100.0%)

No known HIV infection
N=238 (99.2%)

Evaluable best response at index LOT
N=201 (84.5%)

Excluded due to non-conformant data
N=25 (12.4%)

Eligible for study: CIT-treated cohort (3L+)
N=176 (87.6%)

CIT-treated subgroup with prior CAR T-cell therapy (3L+)
N=31 (17.6%)

CIT-treated DLBCL subgroup (3L+)
N=145 (82.4%)

[1] Of the 947 patients initiating 3L+ therapy, 333 (35.2%) received CIT.
[2] The index date was defined as the initiation date of the first treatment in the selected eligible index LOT, starting with 3L+, following the first documentation of a confirmed diagnosis of LBCL.

RESULTS

Baseline characteristics (Table 1)

- Among 176 LBCL patients (75% male) in the 3L+ CIT-treated cohort:
  - Median (range) age was 61.3 (22.4–88.2) years
  - 87% of patients were White; there were no African-American patients
  - 85% had an ECOG-PS score of 0/1
  - 37% had an International Prognostic Index score ≥3 and 73% had Ann Arbor stage III/IV
  - Median (range) number of previous lines of anti-lymphoma therapies was 2 (2–7)
  - 71% had primary refractory disease and 92% were refractory to their most recent anti-CD20 therapy
  - 18% had prior ASCT and 16% had prior CAR T-cell therapy

Table 1. Baseline characteristics of LBCL patients[1]

		Subgroups	
	Overall N = 176	Prior CAR-T N = 31[2]	DLBCL N = 145
Demographics			
Age at index date, years, median (range)	61.3 (22.4–88.2)	60.8 (22.3–89.3)	61.6 (22.2–88.2)
Male sex, n %	132 (75.0)	19 (61.3)	107 (73.8)
Race, n (%)			
White	153 (86.9)	29 (93.5)	124 (85.5)
Asian	6 (3.4)	1 (3.2)	5 (3.4)
Other/Not reported	17 (9.7)	1 (3.2)	16 (11.0)
Clinical characteristics			
ECOG-PS, n %			
0/1	150 (85.2)	25 (80.6)	119 (82.1)
2	26 (14.8)	6 (19.4)	26 (17.9)
Histology subtypes, n %			
DLBCL (de novo or transformed)	145 (82.4)	26 (83.9)	145 (100.0)
DH or TH DLBCL	20 (11.4)	5 (16.1)	0
PMBCL	6 (3.4)	0	0
HGBCL, NOS	5 (2.8)	0	0
IPI risk classification, n %			
0–2	73 (41.5)	12 (38.7)	62 (42.8)
≥3	65 (36.9)	12 (38.7)	54 (37.2)
Ann Arbor disease stage, n %			
Stage I/II	32 (18.2)	5 (16.1)	24 (16.6)
Stage III/IV	129 (73.3)	21 (67.8)	110 (75.9)
Treatment history			
Previous lines of anti-lymphoma therapy, median (range)	2 (2–7)	4 (2–6)	2 (2–7)
Refractory status to most recent prior anti-CD20 therapy, n %	162 (92.0)	31 (100.0)	131 (90.3)
Primary refractory disease, n %	125 (71.0)	27 (87.1)	101 (69.7)
Prior ASCT, n %	32 (18.2)	2 (6.5)	29 (20.0)

Abbreviations: ASCT, autologous stem cell transplantation; CAR T-cell, chimeric antigen receptor T-cell; DH, double-hit; DLBCL, diffuse large B-cell lymphoma; ECOG-PS: Eastern Cooperative Oncology Group performance status; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; PMBCL, primary mediastinal B-cell lymphoma; NOS, not otherwise specified; TH, triple-hit.
[1] Baseline period was defined as the time from the first confirmed disease diagnosis up to and including the date of initiation of the first treatment in a new LOT, starting from 3L+.
[2] 26 Patients (83.9%) had de novo or transformed DLBCL.

Outcomes/clinical endpoints (Table 2 and Figure 2)

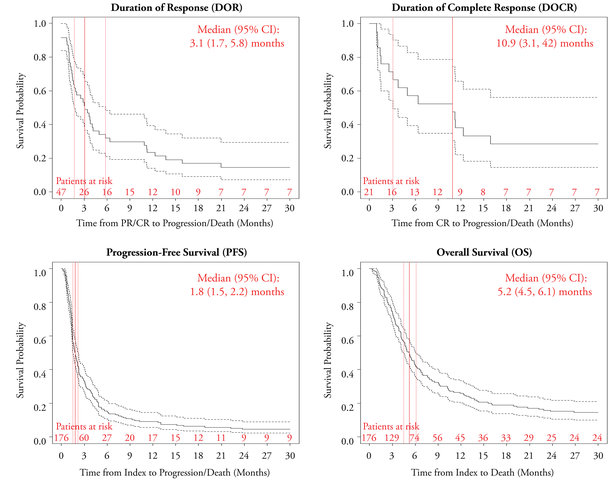
- Among 3L+ CIT-treated patients, ORR was 27% and 12% had a CR.
- Median DOR, DOCR, PFS, and OS were 3.1, 10.9, 1.8, and 5.2 months, respectively.
- Outcomes were consistent for the DLBCL subgroup, and worse for the prior CAR T-cell subgroup.

Table 2. Real-world outcomes of LBCL patients

		Subgroups	
	Overall N = 176	Prior CAR-T N = 31	DLBCL N = 145
ORR, n (%)	47 (26.7)	5 (16.1)	39 (26.9)
CR, n (%)	21 (11.9)	2 (6.5)	16 (11.0)
Time-to-event outcomes, months			
DOR, median (95% CI)	3.1 (1.7, 5.8)	2.9 (1.4, NR)	3.8 (2, 11.3)
DOCR, median (95% CI)	10.9 (3.1, 42)	4.4 (1.4, NR)	11.8 (5, NR)
PFS, median (95% CI)	1.8 (1.5, 2.2)	1.6 (1.1, 3.4)	1.9 (1.6, 2.5)
OS, median (95% CI)	5.2 (4.5, 6.1)	3.6 (2.8, 6.2)	4.9 (4.1, 6.1)

Abbreviations: CAR T-cell, chimeric antigen receptor T-cell; CI, confidence interval; CR, real-world complete response; DLBCL, diffuse large B-cell lymphoma; DOCR, real-world duration of complete response; DOR, real-world duration of response; NR, not reached; ORR, real-world overall response rate; OS, overall survival; PFS, real-world progression-free survival.

Figure 2. Kaplan–Meier curves of time-to-event outcomes in overall 3L+ CIT-treated LBCL patients



CONCLUSION

- Among patients treated with CIT in the 3L+ setting, the proportion of patients with overall response was low.
- DOR, PFS, and OS were short, indicating that CIT confers limited clinical benefit for LBCL in the 3L+ setting.
- The outcomes were worse in the subgroup of patients who previously received CAR T-cell therapy, and were consistent in the subgroup with DLBCL.
- These results underscore an unmet need for novel, more effective treatments for patients with LBCL currently receiving CIT that can improve clinical outcomes.

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