LymphomaHub

DLBCL

R-CHOP *versus* DA-EPOCH-R as frontline therapy for DLBCL: Results from a phase III trial

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On 2 April 2019, Nancy Bartlett from Washington University School of Medicine, St Louis, MO, USA and colleagues, published in the *Journal of Clinical Oncology* results from a phase III clinical trial that compared the efficacy of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for diffuse large B-cell lymphoma (DLBCL).

In this randomized, Alliance/CALGB 50303 study (NCT00118209), the efficacy and safety of DA-EPOCH-R and R-CHOP were compared as frontline treatment for patients with DLBCL. The primary endpoint was progression-free survival (PFS), while secondary endpoints included response rates, overall survival (OS), and safety.

Study design & baseline characteristics

- N = 491 previously-untreated patients with disease stage II–IV DLBCL or stage I primary mediastinal large B-cell lymphoma (PMBCL), were 1:1 randomized to either:
  - DA-EPOCH-R: n = 241 or;
  - R-CHOP: n = 250
- Median time from diagnosis to initiation of therapy:
  - DA-EPOCH-R: 21 days
  - R-CHOP: 18 days
- Median patient age: 58 years
- Baseline characteristics were well balanced between the two arms

	DA-EPOCH-R arm	**R-CHOP arm**
Eastern Cooperative Oncology Group (ECOG) performance status:		
ECOG 0	46.9%	40.6%

ECOG 1	39.8%	47.8%
ECOG 2	13.3%	11.6%
Missing	n = 0	n = 1
International Prognostic Index (IPI) risk groups:		
Low	25.1%	26.6%
Low-intermediate	35.3%	38.6%
High-intermediate	26.0%	24.9%
High	13.6%	10.0%
Missing	n = 6	n = 9

Treatments

- Dosing (six 21-day cycles):
  - DA-EPOCH-R:
    - Etoposide: 50 mg/m^2 daily intravenously (IV) on Days 1, 2, 3, and 4
    - Doxorubicin: 10 mg/m^2 daily IV on Days 1, 2, 3, and 4
    - Vincristine: 0.4 mg/m^2 daily IV on Days 1, 2, 3, and 4
    - Cyclophosphamide: 750 mg/m^2 IV on Day 5
    - Prednisone: 60 mg/m^2 daily, orally on Days 1, 2, 3, 4 and 5
    - Rituximab: 375 mg/m^2 IV on Day 1 prior to EPOCH chemotherapy
    - Dose-adjustment occurred based on absolute neutrophil count (ANC) levels, as previously reported here
  - R-CHOP:
    - Standard dosing
  - Consolidative radiotherapy was not allowed
- Patients who received a full six-cycle treatment:

- DA-EPOCH-R: 82.0%
- R-CHOP: 88.0%

- Reasons for early treatment discontinuation in DA-EPOCH-R *versus* R-CHOP:
  - Disease progression: 1.3% *versus* 8%
  - Adverse events (AEs): 6.3% *versus* 0%
  - Death: 2.5% *versus* 6%
  - Patient withdrawal after initiating treatment: 2.9% *versus* 2%
  - Patient withdrawal before beginning protocol treatment: 1.7% *versus* 4%
  - Alternative therapy: 1.3% *versus* 8%Other missing reasons: 2.9% *versus* 1.6%

Key findings

- At a median follow-up of 5.2 years (range, 4.8–4), 159 patients had a PFS event and 109 died
- There was no statistical difference in PFS between the DA-EPOCH-R and R-CHOP arms (HR = 0.93; [95% CI, 0.68–27]; *P* = 0.65)
- There was no statistical difference in OS between the DA-EPOCH-R and R-CHOP arms (HR = 1.09; [95% CI, 0.75–59]; *P* = 0.64)

	DA-EPOCH-R arm	**R-CHOP arm**	**Full cohort**
Two-year PFS rate	78.9%	75.5%	77.1% (95% CI, 73.5–81)
Five-year PFS rate	68.0%	66.0%	67.1% (95% CI, 62.8–71.6)
Five-year OS rate	77.5%	78.5%	78.0% (95% CI, 74.3–81.9)
Overall response rate	86.7%	88.0%	-
Complete response (CR) and unconfirmed CR (CRu) rate	58.5%	59.6%	-
	P = 0.67		-

- Patients older than 60 years had inferior PFS compared to younger patients (HR = 1.43; [95% CI, 1.04–95]; *P* = 0.26)
- PFS was significantly associated with IPI (*P* < 0.001):
  - For IPI 0–1: two-year PFS was 91.7% (95% CI, 86.9–96.8)
  - For IPI 2: two-year PFS was 76.5% (95% CI, 70.4–83.2)
  - For IPI 3: two-year PFS was 70.7% (95% CI, 63–79.4)
  - For IPI 4–5: two-year PFS was 62.2% (95% CI, 50.7–76.4)
- *Post hoc* subgroup analyses based on age, lactate dehydrogenase levels, ECOG performance status, extranodal disease, and IPI risk, revealed the following statistical differences:
  - PFS was higher in the DA-EPOCH-R arm in patients with high-risk IPI 4–5 (HR = 0.46; [95% CI, 0.21–01]; *P* = 0.052)
  - PFS was higher in the DA-EPOCH-R arm in patients with IPI 3–5 (HR = 0.63; [95% CI, 0.41–99]; *P* = 0.041; Unplanned, not powered analysis)
  - No differences in OS or PFS between arms was observed for any other subgroup analysis
- Central nervous system (CNS) relapse occurred in:
  - DA-EPOCH-R: 3.3% of patients
  - R-CHOP: 4.0% of patients

Safety

- Treatment-related deaths:
  - DA-EPOCH-R: 2.1% (n = 5)
    - Infection: n = 2
    - Cardiac issues: n = 1
    - Sudden death: n = 1
    - Multiorgan failure: n = 1
  - R-CHOP: 2.1% (n = 5)
    - Infection: n = 2
    - Cardiac issues: n = 1
    - CNS hemorrhage: n = 1
    - Unknown: n = 1
  - Grade 3–5 treatment-related AEs occurred in:
    - DA-EPOCH-R: 98.3% of patients
    - R-CHOP: 78.2% of patients
    - Comparison: *P* < 0.001
  - Grade 3–4 treatment-related hematological (97.5% *versus*7%; *P* < 0.001) and non-hematological (72.2% *versus* 43.2%; *P* < 0.001) AEs were more common in the DA-EPOCH-R arm than the R-CHOP arm

- Late cardiac events occurred in:
  - DA-EPOCH-R: n = 2 patients
    - Atrial fibrillation (n = 1)
    - Myocardial infraction with heart failure (n = 1)
  - R-CHOP: n = 6 patients
    - Left ventricular systolic dysfunction (n = 5)
    - Atrial fibrillation (n = 1)

Conclusion

- DA-EPOCH-R was associated with greater toxicity and did not improve PFS, OS or response rate when compared to R-CHOP, as frontline treatment in naïve patients with DLBCL or PMBCL

References

1. Bartlett N.L. *et al.* Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *J Clin Oncol.* 2019 Apr 2:JCO1801994. DOI: 10.1200/JCO.18.01994 [Epub ahead of print].