CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) Compared to CPOP-R (cyclophosphamide, pixantrone, vincristine, prednisone, rituximab) in 1st Line Therapy of Diffuse Large B Cell Lymphoma (DLBCL): An Interim Analysis

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INTRODUCTION

- The CHOP-R regimen is the standard regimen for 1st line therapy of patients with DLBCL.
- Pixantrone (BBR 2778) is a novel aza-anthracenedione with structural similarities to mitoxantrone and with substantially less delayed cardiotoxicity than doxorubicin or mitoxantrone in animal models.
- In a phase 1/2 study of CPOP in 65 patients with relapsed NHL who had received a 1st line therapy regimen, patients received pixantrone at 80 – 180 mg/m^2. This study indicated substantial activity with an overall response rate of 77% and complete response (CR) rate of 54% with acceptable toxicity.[1]
- Studies in indolent NHL demonstrated that the combination of pixantrone with rituximab is well tolerated and more active than rituximab alone.[2]
- The purpose of this phase 1/2 study is to compare CPOP-R to CHOP-R with special regards to safety, activity, and cardiac toxicity and to demonstrate that the response rate is not lower than CHOP-R.
- Efficacy results reported here are from the first 40 patients enrolled. Safety data include preliminary data from 78 patients.

STUDY DESIGN

- Multicenter, open-label study
- Patients will be treated for 4 cycles. Continued treatment is determined by patient response[3] at the end of cycle 4, as follows:
  - Patients who demonstrate PR will receive 4 additional cycles of treatment.
  - Patients who experience CR will receive 2 additional cycles of treatment.
  - Patients who have no response will be discontinued from the study.
- Cardiac scan (MUGA) every 2 cycles
- Responses evaluated using Cheson criteria
- Objective response assessed in cycle 4

TREATMENT

Day	Experimental Arm CPOP-R	Control Arm CHOP-R
1	Cyclophosphamide 750 mg/m^2	Cyclophosphamide 750 mg/m^2
1	Pixantrone 150 mg/m^2	Doxorubicin 50 mg/m^2
1	Vincristine 1.4 mg/m^2	Vincristine 1.4 mg/m^2
1 - 5	Prednisone 100 mg/day orally	Prednisone 100mg/day orally
1	Rituximab 375 mg/m^2	Rituximab 375 mg/m^2

PATIENT CHARACTERISTICS

	Experimental CPOP-R N=21	Comparator CHOP-R N=19
Age, yrs		
Median (range)	70 (38-83)	67 (47-81)
Sex		
Male	15	10
Female	6	9
Baseline IPI Score		
≤ 2	15	9
3 or 4	6	9
5	0	1
ECOG Performance Rating		
0	8	8
1	12	8
2	1	3

ELIGIBILITY

Inclusion Criteria

- Histologically confirmed diffuse large B-cell lymphoma according to REAL/WHO classification
- Stage II, III or IV disease
- Adequate cardiac function: LVEF ≥ 50% by MUGA scan
- CD20+
- ≥ 18 years old; life expectancy of at least 3 months
- Measurable disease
- ECOG performance score of 0, 1, or 2

• Adequate bone marrow function:	-absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L -platelet count ≥ 100 x 10^9/L
• Adequate renal function:	-creatinine ≤ 2.0 x ULN
• Adequate hepatic function:	-bilirubin ≤ 1.5 x ULN -SGOT and SGPT ≤ 2.0 x ULN

Exclusion Criteria

- History of indolent lymphoma
- Active CNS involvement
- HIV-related lymphoma
- Prior radiotherapy or chemotherapy
- Major thoracic and/or abdominal surgery in the preceding 4 weeks from which the patient has not fully recovered
- Clinically significant cardiovascular abnormalities
- CTC grade 3-4 uncontrolled intercurrent infection
- History of, or clinical symptoms suggestive of HIV, HBV, or HCV
- Neurological contraindication to vincristine (e.g. peripheral neuropathy)
- Pregnant or lactating women

SAFETY (preliminary)

- In general, overall adverse events appear balanced between treatment arms.
- No patients in either treatment arm had an adverse event of heart failure reported.
- There were 3 deaths within 30 days of the last dose of study drug on CPOP-R arm. Two of the events were attributed to study treatment (pneumonia concurrent with neutropenia and non-cardiogenic pulmonary edema concurrent with non-neutropenic infection). No deaths within 30 days of the last dose of study drug were reported in the CHOP-R arm.
- Overall rates of infection were similar in the CPOP-R and CHOP-R arms (23% vs. 28%, respectively).
- Transient blue or gray discoloration of skin and blue or green discoloration of urine is a known side effect of pixantrone. Adverse events of skin discoloration have been reported in 8% of patients and chromaturia in 5% of patients receiving CPOP-R.
- No instances of serious or significant hepatic or renal damage related to study therapy have been reported in either treatment arm.

Summary of Adverse Events

	Experimental CPOP-R N=39	Comparator CHOP-R N=39
Patients with adverse events	21 (54%)	24 (62%)
Patients with treatment-related adverse events	21 (54%)	24 (62%)
Patients with grade 3 or 4 adverse events	14 (36%)	18 (46%)
Patients with grade 3 or 4 treatment-related adverse events	12 (31%)	15 (38%)
Patients with serious adverse events	10 (24%)	11 (26%)
Patients with adverse events leading to withdrawal	0	4 (10%)*

*1 patient discontinued due to febrile neutropenia, 1 due to neutropenia, 1 due to neutropenia and paresthesia, and 1 due to fatigue.

Cardiac Safety

- Asymptomatic absolute LVEF declines of ≥ 10% have been reported with equal frequency in both treatment arms.
- The mean decrease in LVEF was similar in both treatment arms (14% in experimental vs. 17% in comparator).

Summary of Decreases in LVEF

Declines in LVEF	CPOP-R	CHOP-R
10% to 15%	6	1
> 15% to 20%	2	5
> 20%	0	2

Select Adverse Events

	Experimental CPOP-R N=39	Comparator CHOP-R N=39
All neutropenia	10 (26%)	11 (28%)
Grade 3/4 neutropenia	9 (23%)	10 (26%)
Leukopenia	7 (18%)	6 (15%)
Grade 3/4 leukopenia	5 (13%)	5 (13%)
Febrile neutropenia	2 (5%)	7 (18%)
Thrombocytopenia	1 (3%)	3 (8%)
Anemia	5 (13%)	8 (21%)
Grade 3/4 anemia	2 (5%)	2 (5%)
Infection	9 (23%)	11 (28%)
≥ grade 3 infection	2 (5%)	7 (18%)
Nausea	7 (18%)	6 (15%)
Esophagitis	1 (1%) grade 1 only	0
Stomatitis	2 (5%) grade 2 only	3 (8%) grade 2 only

TREATMENT RESPONSES

Overall Response Rate (CR+PR) at the cycle 4 assessment was similar between treatment arms.*

	Experimental CPOP-R N=21	Comparator CHOP-R N=19
CR	33%	32%
CR+PR	86%	84%

*Investigator assessment

SUMMARY and CONCLUSIONS

- Based on this preliminary analysis, we conclude that for 1st line therapy of patients with DLBCL, CPOP-R has similar activity to CHOP-R with no more toxicity.
- Cardiac safety, based on reporting of adverse events and LVEF assessment, was similar between treatment arms.
- Further follow-up is required.

References

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Disclosure statement

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