Phase II Study of Pixantrone in Combination with Cyclophosphamide, Vincristine, and Prednisone (CPOP) in Patients with Relapsed Aggressive Non-Hodgkin's Lymphoma

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Presentation does not include discussion of off-label use of a drug or medical device: drug is not yet approved.

Introduction

- Pixantrone (BBR 2778) is a novel aza-anthracenedione with less cardiotoxicity and superior activity when compared with doxorubicin and mitoxantrone in murine leukemia and lymphoma tumor models.
- Pixantrone single agent therapy led to major responses in patients with multiply-relapsed aggressive NHL, including diffuse large B-cell lymphoma.
- Phase I of the current study established the recommended dose (RD) of pixantrone for the phase II portion, reported here.
- In Phase II of this study, 30 patients were treated with the CPOP regimen at the RD of 150 mg/m^2 pixantrone.

Background: Phase I of this CPOP Study N = 35

	Pixantrone Dose (mg/m^2)					
	80	100	120	**150***	180	
Response**						**Total**
CR	2/4	1/3	7/10	5/6	5/12	**20/35 (57%)**
PR	0/4	2/3	3/10	1/6	2/12	**8/35 (23%)**
ORR	2/4	3/3	10/10	6/6	7/12	**28/35 (80%)**

***150 mg/m^2 was the recommended dose for Phase II**
****Per Cheson criteria, response of any duration**

Phase I included 22 patients with diffuse large B-cell lymphoma

Objectives, Phase II CPOP

- To evaluate the efficacy of the CPOP combination therapy in terms of objective response rate (ORR,CR, PR) and duration of response

- To evaluate the safety of the combination therapy in patients with relapsed aggressive non-Hodgkin's lymphoma

Study Design

- International, multicenter, open-label study
- Up to 6 cycles of treatment, or until disease progression, toxicity or withdrawal of consent
- Responses evaluated using Cheson criteria
- Objective response assessed every two cycles

Major Eligibility Criteria

- Adult patients with histologically confirmed relapsed aggressive NHL
- ECOG performance status 0 or 1
- 1 or 2 prior lines anthracycline chemotherapy
- Cumulative dose of doxorubicin equivalent ≤ 450 mg/m^2
- Adequate bone marrow, renal and liver functions
- No recent myocardial infarction
- LVEF ≥ 50%
- No recent radiotherapy or radioimmunotherapy

CPOP Study Regimen

Study Medication	Dose	Day, each 3 week cycle
Cyclophosphamide	750 mg/m^2	1
Vincristine	1.4 mg/m^2	1
Pixantrone	150 mg/m^2	1
Prednisone	100 mg	1-5

Median number of cycles of study drug received: 6 (range 1-6)

Total number of cycles received: 151

Patient Characteristics

No. Patients (ITT population)	30
Age in years, median (range)	66 (26-76)
Sex M/F	18/12
ECOG Performance Status, 0/1	12/18
Pathology	
diffuse large B cell	20 (67%)
follicular grade III	2 (7%)
mantle cell	8 (26%)

Patient Characteristics

Prior Therapy	Number pts (%)
Chemotherapy	30 (100%)
Median prior cumulative doxorubicin dose, mg: 588	
Median number of previous therapy lines: 2 (1–7)	
Median time since last chemotherapy: 14 mo. (1-202)	
Immunotherapy	20 (67%)
Bone marrow transplantation	6 (20%)
Radiotherapy	11 (37%)

Efficacy

N = 30

Response Rate, ITT Population

- CR 14 (47%)
- PR 8 (26%)
- ORR 22 (73%)

Median duration of response: 10.2 months

95% CI: 6.7 – 23 months

Non-Hematological Adverse Events

Event By maximum NCI CTC grade	Grade 3/4 # pts (%)
Metabolic and nutritional (hyperglycemia, 3 pts)	5 (17%)
Gastrointestinal (abdominal pain, 3 pts)	4 (13%)
Infections	4 (13%)
General disorders (asthenia, 2 pts)	3 (10%)
Nervous system (neuropathy, 2 pts)	3 (10%)
Dyspnea	2 (7%)

Non-Hematological Adverse Events: Cardiac Safety

- 4 patients had a decrease in LVEF >10% and ≤ 20% as determined by MUGA-scan
- 1 of these patients also developed symptomatic right heart failure classified by the investigator as related to progressive NHL
- 2 additional patients experienced LVEF decline > 20% during long-term follow up
  - 1 pt was asymptomatic
  - 1 pt was symptomatic but was undergoing high-dose chemo and SCT at the time

Hematological Adverse Events

Event by maximum NCI CTC grade	Grade	
	3	4
	# Pts (%)	
Neutropenia	6 (20%)	23 (77%)
Leukopenia	8 (27%)	19 (63%)
Lymphopenia	16 (53%)	0
Anemia	9 (30%)	0
Febrile neutropenia	6 (20%)	0
Thrombocytopenia	5 (17%)	1 (3%)

Conclusions

- CPOP combination therapy with 150 mg/m^2 pixantrone results in a high overall response rate (73%) with 47% complete responses (51% CR in Phase I of the study).
- The regimen exhibits an acceptable toxicity profile and can be administered safely in an outpatient setting even in this cohort of elderly, anthracycline-pretreated patients.

Phase II comparative study in progress

An international phase II study (CPOP-Rituximab versus CHOP-Rituximab in the first line treatment of Diffuse Large B Cell NHL) has been initiated and is currently recruiting. The following map shows active and potential sites for this study.


Canada
USA
Mexico
Colombia
Ecuador
Peru
Argentina
France
Germany
Ukraine
Russia
Bulgaria