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Results of a phase I study of Bendamustine in Combination with Ofatumumab, Carboplatin and Etoposide (BOCE) for Refractory of Relapsed Aggressive B-cell Non Hodgkin's Lymphomas (NHL)

Sameh Gaballa, MD
Thomas Jefferson University Hospital, samehgaballa@gmail.com

Neil D. Palmisiano, MD
Thomas Jefferson University, Neil.Palmisiano@jefferson.edu

Aakanksha Asija, MD
Thomas Jefferson University, aakanksha.asija@jefferson.edu

Andrew Chapman, DO
Thomas Jefferson University, andrew.chapman@jefferson.edu

Jennifer K. Cloud, BS
Thomas Jefferson University, Jennifer.cloud@jefferson.edu

See next page for additional authors

Authors
Sameh Gaballa, MD; Neil D. Palmisiano, MD; Aakanksha Asija, MD; Andrew Chapman, DO; Jennifer K. Cloud, BS; Joanne Filicko-O'Hara, MD; Lewis Rose, MD; Michael Ramirez, MD; Onder Alpdogan, MD; Neal Flomenberg, MD; Barbara Pro, MD; Elena Gitelson, MD, PhD; and Mark Weiss, MD

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Department of Medical Oncology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Introduction

- There are a number of regimens used to treat relapsed/ refractory aggressive lymphomas and little consensus exists on the best salvage treatment.
- No regimen has shown clear superiority but uniformly there was an inferior outcome among patients who had relapsed after a prior rituximab containing regimen.
- **Ofatumumab** is a fully human IgG1κ monoclonal anti-CD20 antibody. It recognizes a distinct epitope on the human CD20 molecule. *In vitro* studies with ofatumumab have shown more complement dependent cytotoxicity than rituximab.
- **Bendamustine** has single agent activity in relapsed aggressive lymphomas and has a favorable safety profile.

Objectives

- We conducted a **phase I trial** using a novel RICE-like salvage combination regimen in which **ofatumumab** is substituted for rituximab and **bendamustine** replaces ifosfamide in combination with **carboplatin** and **etoposide** (BOCE) to assess the safety and toxicity profile of this combination.
- The objective from the phase I part of this trial was to **assess safety and tolerability** of this combination.

Methods

- **Eligibility**:
  - Relapsed or refractory aggressive B cell lymphoid malignancies after at least one prior chemotherapy regimen
  - Measurable disease and adequate organ function.
- **Design**:
  - **Standard 3+3 design** using escalated doses of **bendamustine** [70, 90, and 120 mg/m2 Day (D) 1-2], fixed doses of **ofatumumab** (cycle 1: 300 mg D1, 1000mg D3, cycle 2 and 3: 1000mg D1), **Carboplatin** (Carboplatin AUC 5 D2) and **Etoposide** (100mg/m2 D 1-3).
  - All patients received **growth factor** support.
  - Patients were evaluated for response after cycle 2 with a CT scan and after cycle 3 with a PET-CT scan.
  - The first cycle was administered in the inpatient setting, while subsequent cycles were administered in the outpatient department.

Patient Characteristics

	Age	Sex	Diagnosis	Disease Status	sAAIPI	No. of Prior Therapies	Last Therapy Received	No of Cycles Received	Bendamustine dose (mg/m^2)	Response
Patient 1	72	Male	DLBCL	Refractory	High-intermediate	2	R-Bendamustine	3	70	PD
Patient 2	62	Male	DLBCL	Refractory	Low-intermediate	1	R-CHOP	3	70	SD
Patient 3	63	Male	Follicular G3A	Relapsed	Low-intermediate	2	R-CHOP	3	70	PD
Patient 4	62	Male	Follicular G3B	Relapsed	High risk	3	R-Bendamustine	1	70	NA
Patient 5	75	Female	Mantle cell lymphoma	Relapsed	Low-intermediate	1	R-CHOP	3	70	CR
Patient 6	54	Female	DLBCL	Relapsed	High-intermediate	2	R-CHOP	3	90	PR
Patient 7	53	Male	Follicular G3B	Relapsed	Low-intermediate	1	R-CHOP	3	90	CR
Patient 8	56	Male	Transformed CLL	Refractory	Low-intermediate	2	R-CHOP	3	90	CR
Patient 9	57	Female	DLBCL	Refractory	High-intermediate	1	R-CHOP	2	120	CR
Patient 10	63	Male	DLBCL	Refractory	High-intermediate	3	R-CHOP	3	120	PR
Patient 11	65	Female	Follicular G3B	Relapsed	Low-intermediate	1	R-CHOP	3	120	CR

All patients with refractory disease were refractory to rituximab.
All patients had stage III or IV disease.

Regimen Saftey

Grade III-IV toxicity	
Neutropenia	n= 9 (82%)
Thrombocytopenia	n= 7 (64%)
Anemia	n=7 (64%)
Lymphopenia	n= 3 (27%)
Febrile Neutropenia	n= 3 (27%)
Hyponatremia	n=2 (18%)
Hypophosphatemia	n=2 (18%)

- Incidence of non-hematologic toxicity was in line with other carboplatin based regimens
- **Dose limiting toxicity** was not reached.
- **Six** serious adverse events (**SAEs**) were reported in 4 patients and included:
  - Acute kidney injury, urinary tract infection, pleural effusion, lower GI bleeding, thromboembolic event and febrile neutropenia
- **3 patients required hospitalization** within 30 days from the chemotherapy cycle.
- **No patient** discontinued therapy due to **toxicity**.
- **Infusion related reactions** occurred in **27%** of patients and were **all grade I-II.**

- After 3 BOCE cycles, **overall response rate was 64%** [**CR**: 5 patients (**46**%); **PR**: 2 patients(**18**%)].
- Two patients (**18**%) **had progressive disease** and 1 patient (**9**%) had **stable disease**. One patient was not evaluable for response.
- Five patients (**46**%) subsequently underwent an **allogeneic transplant.**
- Five patients (**45**%) **eventually died**, all of **progressive disease**.

Conclusions

- The BOCE regimen is **well tolerated** in patients with relapsed or refractory aggressive B cell lymphomas
- An important benefit of this regimen compared to most salvage therapies is that this regimen can be largely **administered in the outpatient setting.**
- Most responses were seen at the 90 mg/m^2 and 120 mg/m^2 in this small phase I cohort.
- Bendamustine at the dose of 120 mg/m^2 is currently being utilized in the **phase II** portion of the trial which is ongoing to assess efficacy.