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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)

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

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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.

Regimen Safety

<table>
<thead>
<tr>
<th>Grade III-IV toxicity</th>
<th>No. of Patients (with 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>n= 9 (82%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>n= 7 (64%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>n=7 (64%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>n= 3 (27%)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>n= 3 (27%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>n=2 (18%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>n=2 (18%)</td>
</tr>
</tbody>
</table>

- 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 required hospitalization due to toxicity.
  - Infusion related reactions occurred in 27% of patients and were all grade 1-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/m2 and 120 mg/m2 in this small phase I cohort.
- Bendamustine at the dose of 120 mg/m2 is currently being utilized in the phase II portion of the trial which is ongoing to assess efficacy.

Patient Characteristics

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Disease Status</th>
<th>sAAIPI</th>
<th>No. of Prior Therapies</th>
<th>Last Therapy Received</th>
<th>No. of Cycles Received</th>
<th>Bendamustine dose (mg/m2)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>Male</td>
<td>DLBCL</td>
<td>Refractory</td>
<td>High-intermediate</td>
<td>2</td>
<td>R-Bendamustine</td>
<td>3</td>
<td>70</td>
<td>PD</td>
</tr>
<tr>
<td>62</td>
<td>Male</td>
<td>DLBCL</td>
<td>Refractory</td>
<td>Low-intermediate</td>
<td>1</td>
<td>R-CHOP</td>
<td>3</td>
<td>70</td>
<td>SD</td>
</tr>
<tr>
<td>63</td>
<td>Male</td>
<td>Follicular G3A</td>
<td>Relapsed</td>
<td>Low-intermediate</td>
<td>2</td>
<td>R-CHOP</td>
<td>3</td>
<td>70</td>
<td>PD</td>
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<tr>
<td>62</td>
<td>Male</td>
<td>Follicular G3B</td>
<td>Relapsed</td>
<td>High risk</td>
<td>3</td>
<td>R-Bendamustine</td>
<td>1</td>
<td>70</td>
<td>NA</td>
</tr>
<tr>
<td>75</td>
<td>Female</td>
<td>Mantle cell lymphoma</td>
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<td>Low-intermediate</td>
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<td>R-CHOP</td>
<td>3</td>
<td>70</td>
<td>CR</td>
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<tr>
<td>54</td>
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<td>3</td>
<td>90</td>
<td>PR</td>
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<tr>
<td>53</td>
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<td>Follicular G3B</td>
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<td>Low-intermediate</td>
<td>1</td>
<td>R-CHOP</td>
<td>3</td>
<td>90</td>
<td>CR</td>
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<tr>
<td>56</td>
<td>Male</td>
<td>Transformed CLL</td>
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<td>Low-intermediate</td>
<td>2</td>
<td>R-CHOP</td>
<td>3</td>
<td>90</td>
<td>CR</td>
</tr>
<tr>
<td>57</td>
<td>Female</td>
<td>DLBCL</td>
<td>Refractory</td>
<td>High-intermediate</td>
<td>1</td>
<td>R-CHOP</td>
<td>2</td>
<td>120</td>
<td>CR</td>
</tr>
<tr>
<td>63</td>
<td>Male</td>
<td>DLBCL</td>
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<td>High-intermediate</td>
<td>3</td>
<td>R-CHOP</td>
<td>3</td>
<td>120</td>
<td>PR</td>
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<tr>
<td>65</td>
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<td>Low-intermediate</td>
<td>1</td>
<td>R-CHOP</td>
<td>3</td>
<td>120</td>
<td>CR</td>
</tr>
</tbody>
</table>

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