Results of a Phase I/II Trial of Pixantrone (BBR 2778) in Combination with Fludarabine, Dexamethasone and Rituximab (‘FPD-R’) in the Treatment of Patients with Relapsed/Refractory Indolent Non-Hodgkin’s Lymphoma (NHL)

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INTRODUCTION

- The fludarabine-mitoxantrone-dexamethasone-rituximab (FND-R) regimen has significant activity in patients with untreated and relapsed indolent B cell lymphoma.
- Pixantrone (BBR 2778) is a novelaza-aneurinetradeceptor with substantially less delayed cardiotoxicity than doxorubicin or mitoxantrone in animal models.
- Pixantrone has superior activity against murine lymphoma and leukemia in vivo models when compared with doxorubicin or mitoxantrone.
- The current study substituted pixantrone for mitoxantrone in the combination therapy FND-R (FPD-R).
- Patients with indolent NHL and patients with aggressive NHL have responded to treatment with pixantrone.
- Indolent relapsed/refractory NHL: pixantrone + rituximab vs. rituximab:
  - Time to tumor progression (TTP): pixantrone + rituximab: 365 days
  - TTP, rituximab: 245 days (log-rank p-value < 0.001)
- Overall response rate (ORR): pixantrone + rituximab: 75%, CR 35%
- ORR, rituximab: 33%, CR 11%
- Aggressive NHL: COPP - cyclophosphamide, vincristine, procarbazine, and prednisone (ORR = 40% vs. 20%)

OBJECTIVES

- To determine the recommended dose (RD) of pixantrone when substituting for mitoxantrone in the FND-R regimen (FPD-R).
- To evaluate the safety and efficacy of this regimen in patients with relapsed or refractory indolent NHL.

STUDY DESIGN

- Multicenter, open-label study
- Up to 8 cycles, or until disease progression, toxicity or withdrawal of consent
- Cardiac scan (MUGA) every two cycles
- Responses evaluated using Cheson criteria
- Objective response assessed every two cycles

Study Treatment Schedule

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Pixantrone</td>
<td>80 mg/m²</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Pixantrone</td>
<td>120 mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Fludarabine</td>
<td>25 mg/m²</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Fludarabine</td>
<td>25 mg/m²</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Rituximab</td>
<td>375 mg/m²/day</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Rituximab</td>
<td>375 mg/m²/day</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>Rituximab</td>
<td>375 mg/m²/day</td>
</tr>
</tbody>
</table>

TREATMENT RESPONSES

Overall Response Rate in Evaluable Population: 89%

- Response: Complete Response (CR) 17 (63)
- Partial Response (PR) 5 (18)
- Overall Response (CR+PR) 22 (79)

PATIENT CHARACTERISTICS

| Patients entered / safety / efficacy evaluable* | 29 / 28 / 27 |
| Age in years, median (range) | 63 (32-78) |
| WHO Performance Status 0 / 1 | 15 / 14 |

Prior Therapies

- Pixantrone: 29 patients
- Fludarabine: 29 patients
- Dexamethasone: 28 patients
- Rituximab: 29 patients

Pathology

- Follicular center cell grade 1/2: 18
- Small lymphocytic: 6
- Lymphoplasmacytoid: 1
- Marginal zone: 3
- Diffuse large B cell (protocol violation): 1

Drug Administration

- Median number of cycles per patient (range) = 5 (1 – 8)
- At the 120 mg/m² dose level, a total of 108 cycles of study therapy were given.

SAFETY

- No dose limiting toxicity reported in the 3 patients treated at 80 mg/m².
- Grade 4 neutropenia for 7+ days in 1 of the 6 initial patients at 120 mg/m². This dose level was assessed as the recommended dose in the FPD-R combination, without further escalation.

Treatment-related Grade 3 / 4 Adverse Events Occurring in ≥ 2 pts*

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lympohopenia</td>
<td>25</td>
<td>0</td>
<td>25 (90%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14</td>
<td>8</td>
<td>22 (79%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12</td>
<td>11</td>
<td>23 (82%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>1</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Infection</td>
<td>6</td>
<td>0</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>0</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Hypersplenism</td>
<td>3</td>
<td>0</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Wound/abdominal wound</td>
<td>3</td>
<td>0</td>
<td>3 (11%)</td>
</tr>
<tr>
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<td>0</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>0</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Bronchitis</td>
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<td>0</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Cough</td>
<td>2</td>
<td>0</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

Cardiac Safety

- A total of 7 of 28 (25%) patients evaluable for safety had a decline in LVEF ≥ 20% to ≤ 40%.
- No patient had a decline in LVEF > 40%.

- Median duration of response: 25 months (Kaplan-Meier estimate)
- Range 2.4 to 43 months
- Five responders went on to BMT

SUMMARY and CONCLUSIONS

- The RD of pixantrone in the FPD-R regimen was 120 mg/m².
- The primary toxicity was hematologic; no serious cardiotoxicity was observed.
- This treatment is highly active and is associated with major, durable responses; the overall response rate was 89%.
- The regimen can be given on an outpatient basis and is generally well tolerated in relapsed and refractory indolent NHL patients.

Disclosure statement

In compliance with ACCME policy, ASH requires the following disclosures for Dr. L. Fayad: Research Support: Cell Therapeutics, Inc.; A. Santoro, J. Voglova, N. Gabrail, T. Ciuleanu, M. Liberati, B. W. Hancock, S. Stromatt, and D. Caballero. Comparative trial of BBR 2778 (pixantrone) + rituximab vs single agent rituximab in the treatment of relapsed/refractory indolent non-Hodgkin’s lymphoma (NHL). J Clin Oncol (Meeting Abstracts) 2006 24: 7578

REFERENCES