Pegylated liposomal doxorubicin in combination with dexamethasone and bortezomib (VMD) or lenalidomide (RMD) in multiple myeloma pretreated patients

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Abstract: 

Response to Reviewers: Dear Editor,

I'm submitting the revised version of the letter

Comments to the paper:
1) As the reviewer suggested, I omitted the last sentence of the paper

I hope that you'll find it suitable to be published on your journal

Kind regards

Gabriele Buda
Pegylated Liposomal Doxorubicin in combination with Dexamethasone and Bortezomib (VMD) or Lenalidomide (RMD) in Multiple Myeloma pretreated patients

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Waterman et al recently showed that a modified regimen of pegylated liposomal doxorubicin (PLD), bortezomib, and dexamethasone is effective and well tolerated in the treatment of relapsed or refractory multiple myeloma (1). We really appreciated these data that were similar to results that we already described in similar patients (2). We treated a total of 25 patients (11 females and 14 males) with a median age of 61 years at diagnosis (range: 40–69) who were resistant/relapsed after at least one prior therapy. The scheme therapy was based on VMD: bortezomib: 1.3 mg/m² as intravenous bolus twice a week for 2 weeks (on days 1, 4, 8 and 11 of each cycle) in a 28-day cycle for a total of 4 cycles; oral dexamethasone (24 mg) on the day of each bortezomib dose and the day after, and PLD (Myocet®)(30 mg/m²) on day 4 of each cycle, 1 h after bortezomib infusion. Baseline characteristics are shown in table 1. All 25 patients were evaluable for response. Response rates following VMD showed: 2 patients in nCR (10%), 4 in VGPR (20%), 14 in PR (70%) resulting in an overall response rate (ORR) of 80%. Global toxicities were lower and included neutropenia (12.5%), fatigue (25%), thrombocytopenia (25%) and neuropathy (37.5%).

We also treated 14 different patients with of a combination regimen of lenalidomide (25mg d 1-21), PLD and dexamethasone (RMD), 11 patients between 44 and 76 (median age 65) were eligible for evaluation. All the patients had multiple myeloma with Durie-Salmon stage II or III and were resistant or progressed progression after 1 to 5 previous anti-myeloma regimens. RMD was administered for six 28-day cycle. PLD (Myocet®) 30 mg/m² d4, Dex 40 mg d1-4 and 17-20. eight of eleven patients (73%) achieved an objective response to therapy.

Respectively, 2 patients (25%) a VGPR and additional 6 patients (75%) a PR. The most common side effects was haematological toxicity with grade 3/4 neutropenia (48%), thrombocytopenia (38%) and anemia (16,6%). Under thrombosis prophylaxis with aspirin 100 mg per day we observed thrombembolic complications in only in one patients (4,5%). Other non haematological side effects were pain (grade 3/4 - 1 patient), infection (grade 3/4 - 1 patients), diarrhoea (grade 3/4 - 2 patient). Neither neurotoxicity nor constitutional symptoms of grade 3/4 was found.

In our study, lenalidomide or bortezomib in combination with PLD and dexamethason has shown encouraging activity in heavily pretreated patients with relapsed or refractory multiple myeloma. These schemes can be additional standard of care in the treatment of patients with relapsed or refractory multiple myeloma who have received at least one prior therapy (3). The addition of PLD can play a key role in overcoming anthracycline resistance and improving the quality of response without limiting toxicity. The pharmacology of PLD gives rise to a compound with major advantages that could potentially improve response and decrease toxicity. Because increased angiogenic activity occurs in the bone marrow of patients with multiple myeloma, this pegylated formulation can enhance the delivery of doxorubicin to the tumour site. In addition, because myeloma cells divide slowly, the increased exposure of these cells to doxorubicin has the potential of overcoming resistance and increasing tumour cell killing capacity, theoretically resulting in improved response rates (4).
### Table I. Characteristics of MM Patients undergoing VMD or RMD therapy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (median and range)</td>
<td>65 (44–76)</td>
</tr>
<tr>
<td>Number of patients</td>
<td></td>
</tr>
<tr>
<td>VMD</td>
<td>25 (14M, 11F)</td>
</tr>
<tr>
<td>RMD</td>
<td>14 (10M, 4F)</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Durie-Salmon (II/III)</td>
<td>10/29</td>
</tr>
<tr>
<td>Prognostic Markers</td>
<td></td>
</tr>
<tr>
<td>β2-microglobulin (μL)</td>
<td>2.2 (1.1 – 35)</td>
</tr>
<tr>
<td>Creatinin (mg/dl)</td>
<td>0.9 (0.5 – 4.4)</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>4.0 (2.1 – 4.9)</td>
</tr>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>11.3 (5.7 – 16.4)</td>
</tr>
</tbody>
</table>

*a*Median (Range)
References

1 Waterman GN, Yellin O, Swift RA, Mapes R, Eades B, Ackerman E, Berenson JR. A modified regimen of pegylated liposomal doxorubicin, bortezomib, and dexamethasone is effective and well tolerated in the treatment of relapsed or refractory multiple myeloma. Ann Hematol. 2010 Sep 1


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