To determine the tolerability of 3 mL at each subsequent visit, nurses assess the systemic reactions and injection site reactions (ISRs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4: grade 1, tenderness with or without associated symptoms; grade 2, pain, lipoedema, ecchymosis, or phlebitis; grade 3, ulceration, necrosis, severe tissue damage, or any indication for operative intervention; grade 4, injection site reactions with life-threatening consequences. The institutional research ethics board had approved this research study.

Background

Until recently, intravenous (IV) injection has been the standard for bortezomib (btz) administration, with adoption of subcutaneous (SC) injection based on similar efficacy, decreased neuropathy and ease of administration. The product monograph for Bortezomib [Velcade] recommends that IV injections be prepared at a concentration of 1 mg/mL, while SC injections may be prepared at a concentration of 2.5 mg/mL. Many institutions’ and SC administration guidelines use 2 mL as the maximum SC injection volume, although there is no good evidence to support this practice. This would mean that many btz patients will receive 2 injections during each visit with common dosing parameters.

Objectives

- To determine the tolerability of 3 mL maximum volume per subcutaneous injection
- To determine the incidence and grading of injection site reactions (ISRs)
- To determine systemic reactions and, in particular, changes in blood pressure associated with SC injection.

Methods

- At Princess Margaret Cancer Centre from September to December 2012, all consecutive multiple myeloma patients previously on IV btz or receiving btz for the first time received SC btz at a 1 mg/mL concentration, with a maximum of 3 mL injected into each SC injection site. If btz doses were higher than 3 mg (3mL), then the dose was split in half as two SC injections.
- Patients with amyloidosis or patients already on IV btz who required IV hydration with over 2 mLs.
- Injection sites were documented and were alternated between the right/left abdomen, upper/lower quadrant, or right/left thigh.
- At each subsequent visit, nurses assess the previous injection site(s) for any redness, swelling, or pain and take patient’s history.
- Patient’s baseline blood pressure (pre injection) and blood pressure 30 minutes after injection were also noted.
- ISRs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4: grade 1, tenderness with or without associated symptoms; grade 2, pain, lipoedema, ecchymosis, or phlebitis; grade 3, ulceration, necrosis, severe tissue damage, or any indication for operative intervention; grade 4, injection site reactions with life-threatening consequences.
- The institutional research ethics board had approved this research study.

Results

57 individual patients received a total of 339 doses of SC btz. Details of ISR incidence and grading is shown in Figure 1. ISRs were noted in 114 doses (41%) with all reactions being grade 1 or 2. Overall, patients tolerated SC injections well, and only 4 patients were switched back to IV for the following reasons: 1) persistent/ progressive grade 2 skin reactions; 2) nausea; 3) patient preference; 4) discomfort at the injection site.

The incidence of ISRs are similar for injections into the abdomen and thigh with no clear association with volumes injected for grade 1 ISR (Figure 2). However, the 4 cases of Grade 2 reactions were only noted with injection volumes of over 2 mLs.

Baseline and post-administration blood pressure documented in 319 and 300 visits respectively. Most patients had a minimal change in blood pressure 30 minutes post injection (Figure 3). There were no cases of clinically symptomatic hypotension requiring hydration.

With the maximum volume per injection site of 3 mLs, a total of 5 patients received 2 injections per visit (btz dose over 3 mg). If the maximum volume for injection was kept at 2 mLs, a total of 46 patients would receive 2 injections per visit.

Conclusion

- This is the first time that SC btz of a volume up to a maximum of 3 mL (or 3 mg of btz) per injection site has been accepted now as standard of care in our centre, and patients are not asked to wait post-SC injection after the first dose.

References


Acknowledgements: We would like to thank the team of Chemotherapy Daycare nursing staff and pharmacists, Aaron Lo for their dedication and collaboration in this project.

Figure 1 – ISR Incidence and Grading

<table>
<thead>
<tr>
<th>ISR Incidence (n, %)</th>
<th>Site Type</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Abdomen</td>
<td>110</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>Thigh</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Abdomen</td>
<td>109</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Thigh</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Abdomen</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Thigh</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Abdomen</td>
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<td>1</td>
</tr>
</tbody>
</table>

Figure 2 – ISR incidence vs. region and volume injected

<table>
<thead>
<tr>
<th>ISR (Grade)</th>
<th>ISR (Grade 2)</th>
<th>ISR (Grade 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Thigh</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

Figure 3 – Histogram of Changes in BloodPressure 30 Minutes Post-Injection

- Systolic Blood Pressure
- Diastolic Blood Pressure

Change in Blood Pressure (mmHg)

- 0 - 20
- 20 - 40
- 40 - 60
- 60 - 80
- 80 - 100
- 100 - 120
- 120 - 140
- 140 - 160
- 160 - 180

Abdomen

- 0 - 20
- 20 - 40
- 40 - 60
- 60 - 80
- 80 - 100
- 100 - 120
- 120 - 140
- 140 - 160
- 160 - 180

Thigh

- 0 - 20
- 20 - 40
- 40 - 60
- 60 - 80
- 80 - 100
- 100 - 120
- 120 - 140
- 140 - 160
- 160 - 180