Stability of 1.0 and 2.5 mg/mL Bortezomib In Vials and Syringes Following Reconstitution with Sodium Chloride at 4^{0}C and 23^{0}C.

Scott E. Walker[2,3], Lauren F. Charbonneau[1] Ivan Tyono[1] and Shirley Law[2]

[1]Odette Cancer Centre Department of Pharmacy, [2]Sunnybrook Health Sciences Centre Department of Pharmacy, and the [3]Faculty of Pharmacy, University of Toronto, Toronto, Ontario.

INTRODUCTION

Bortezomib is the backbone of various treatment regimens used to treat multiple myeloma both in the first line setting (stem cell transplant and non stem cell transplant candidates) and in the relapsed/refractory setting. It is available in Canada as 3.5 mg of sterile lyophilized powder in a 10-mL clear glass vial, intended for reconstitution with 0.9% sodium chloride (NS).

A 2008 CJHP publication demonstrated that 1.0 mg/mL solutions of bortezomib (Velcade®) retained more than 95% of the initial concentration for up to 42 days when stored at either 4C or 25 C.

However, a May 2011 report in Lancet Oncology demonstrated that subcutaneous bortezomib has an improved safety profile and similar efficacy compared to IV administration in 222 myeloma patients in the relapse setting.

A 2014 CJHP publication demonstrated that 2.5 mg/mL solutions of bortezomib (Velcade® retained more than 95% of the initial concentration for up to 21 days when stored at either 4C or 25 C.

The introduction of a generic version of bortezomib (TEVA) in 2015 raised questions of the stability of the generic formulation and the validity of extending stability from one brand to another. TEVA's generic version of bortezomib is reported to be pharmaceutically similar to VELCADE® and is intended to also be reconstituted with saline. Since stability over a relatively short period of time (14 days) is driven largely by pH, we were interested in completing this evaluation to begin to assess the need to complete stability studies in pharmaceutically similar generic products.

OBJECTIVES

It was the objective of this study to evaluate the stability of bortezomib 1.0 and 2.5 mg/mL solutions stored in the original manufacturer's vial or syringes following reconstitution of the 3.5 mg vial with 0.9% sodium chloride (NS) over 42 days.

The concentration of bortezomib in vials and syringes was evaluated during storage at each temperature using a validated, stability indicating, liquid chromatographic method using UV detection.

NONE of the authors of this poster have any personal or financial relationships with any commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
The bortezomib used in this study was provided by TEVA.

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 15% methanol and 85% 0.04 mol/L potassium phosphate monobasic buffer (pH of 7) which was pumped through 15 cm x 4.6 mm reverse-phase C18, 3-µm column (Supelcosil; Supelco, Toronto, Ontario) at 1.0 mL/min.

Assay Validation

The previously published method was re-evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating bortezomib from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

Stability Study: Vials and Syringes at 4C and 25C.

On study day 0, 24 x 3.5mg vials of bortezomib (TEVA; Lot: 1590615; Expiry: 06 - 2018) were each reconstituted with sodium chloride. The contents of 9 vials were each reconstituted with 3.5 mL of NS to prepare 1 mg/mL solutions in 6 Manufacturer's vials and 6 x 3mL Equashield® syringes containing 1.75 mL. The contents of a further 12 vials were each reconstituted with 1.4 mL of NS to prepare 2.5 mg/mL solutions in 6 Manufacturer's vials and 6 x 3mL Equashield® syringes containing 1.4 mL. 3 of each container (vials and syringes) were stored at room temperature and 3 were stored in the refrigerator. Concentration and physical inspection were completed on study days 0, 1, 3, 7, 10, 14, 22, 28, 34 and 42. The bortezomib concentration was determined by the validated liquid chromatographic method with UV detection at 270 nm.

Data Reduction and Statistical Analysis

The concentration of a solution on a particular day was considered "acceptable" or "within acceptable limits" if it was greater than 90% of the initial concentration (as determined on day 0) and the amount found on that day, with 95% confidence, was also greater than 90% of the initial concentration. Analysis of variance was used to test differences in degradation rate between the different storage temperatures and container combinations. The 5% level was used as the a priori cut-off for significance.

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CONCLUSIONS

We conclude that 3.5-mg TEVA vials of bortezomib reconstituted with 1.4 mL of NS to create a 2.5 mg/mL solution or 3.5 mL of NS to create a 1.0 mg/mL solution are physically and chemically stable for at least 42 days at 4C or room temperature in both Equashield® syringes and the original manufacturer's glass vial.

TEVA's generic version of bortezomib is reported to be pharmaceutically similar to VELCADE® and this study demonstrates that the chemical stability of the TEVA formulation is similar to the stability of the VELCADE® formulation previously reported.

RESULTS

Table 1. Percent Remaining of the Initial Bortezomib Concentration.

Study Day	Vial 4C 1mg/mL	Vial RT 1mg/mL	Syringe 4C 1mg/mL	Syringe RT 1mg/mL	Vial 4C 2.5mg/mL	Vial RT 2.5mg/mL	Syringe 4C 2.5mg/mL	Syringe RT 2.5mg/mL
0	100.000	100.000	100.000	100.000	100.000	100.000	100.000	100.000
1	100.214	99.951	100.364	97.891	100.348	99.635	100.875	102.555
3	99.815	100.909	100.543	98.447	100.506	100.184	100.316	99.590
7	99.498	100.946	101.110	98.805	100.936	100.260	100.273	99.890
10	100.289	102.976	102.296	99.376	101.168	99.630	100.416	99.412
14	102.886	100.985	101.871	99.227	100.389	99.495	99.385	99.907
22	99.211	96.630	99.864	96.077	96.747	98.209	97.806	98.362
28	97.576	98.769	98.460	98.645	97.187	98.198	99.258	98.503
34	97.216	96.960	99.688	97.129	96.617	97.504	99.429	95.531
42	96.523	94.948	98.147	95.975	97.149	96.731	98.766	95.616
Degradation Rate (%/day)	**-0.091**	**-0.133**	**-0.058**	**-0.065**	**-0.110**	**-0.081**	**-0.044**	**-0.128**
T-90 Days	109.94	75.09	172.09	154.29	90.56	124.02	229.36	78.21
Shortest T-90 (95% CI) days	**62.15**	**46.45**	**87.60**	**83.65**	**60.27**	**100.88**	**125.74**	**55.56**

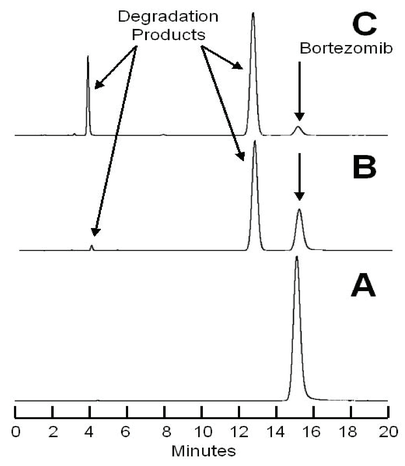

Figure 1.
Chromatogram A represents a solution of 1.0 mg/mL bortezomib in water prior to the addition on sodium hypochlorite. Chromatogram B was chromatographed immediately after the addition of 5uL of 0.3% sodium hypochlorite. 29% of the initial bortezomib was observed to remain. Chromatogram C was chromatographed immediately after the addition of 5uL of 0.4% sodium hypochlorite. 12% of the initial bortezomib was observed to remain. Degradation products appear at 3.7 and 13.5 minutes. Additional products appeared at 4.3, 4.8, 8.7 and 29 minutes.

Assay Validation

Assay validation demonstrated that degradation products are separated from bortezomib (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 2.20% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 1.02% within a day and 0.96% between days.

Concentration Results

Concentrations on each study day are reported in Table 1. During the study period all solutions retained more than 95% of the initial concentration in vials and syringes at both temperatures and concentrations. The calculated use-before-date, with 95% confidence, exceeded 42 days for all temperatures, concentrations and container combinations.

Analysis of variance revealed significant differences in percent remaining due to study day ($p < 0.001$) and temperature ($p = 0.003$), but not container ($p = 0.78$) or concentration ($p = 0.72$). The study was capable of detecting a 0.6% difference in concentration due to study day, temperature, concentration or container. The average difference due to temperature is 0.7% which translates into ~ less than a 2% difference on day 42.