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# Weekly as Opposed to Bi-Weekly Bortezomib as Part of Induction Chemotherapy in Newly Diagnosed Multiple Myeloma is Better Tolerated and Equally Efficient in Terms of Initial Therapeutic Response: Real-World Data from a Retrospective Audit

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**Abstract**

Bortezomib is a proteasome inhibitor that has shown efficacy in the treatment of newly diagnosed multiple myeloma. The VTD (Bortezomib, Thalidomide, Dexamethasone) triplet chemotherapy regime is frequently used as induction prior to autologous stem cell transplant, in line with national and international recommendations.

The manufacturer's protocol for Bortezomib recommend a twice weekly dosing schedule. Adverse effects are common, most notably peripheral and autonomic neuropathy. These adverse effects can be disabling, even at lower grades and often limit drug tolerance.

We propose a once weekly Bortezomib treatment regime as an alternate modus operandi. Here we use real-world data to demonstrate that weekly compared to bi-weekly Bortezomib is better tolerated whilst achieving similar outcomes in terms of initial therapeutic response. We demonstrate a trend of lower incidence of neuropathy- both peripheral and autonomic- with the weekly regime. There was also a trend of fewer serious adverse events with the weekly regime with lower rates of hospital admissions due to infections. In addition, we show that this regime is associated with better Thalidomide tolerance. We believe that delivery of Bortezomib through a weekly regime facilitates patients being able to maintain on Bortezomib longer and receive higher cumulative doses.

**Keywords:** Multiple Myeloma, Plasmacytoma, Induction, Response, Bortezomib, Peripheral Neuropathy

## Abbreviations

CI: Confidence Intervals; CR: Complete Response; CTCAE: Common Terminology Criteria for Adverse Events; CyBorD: Cyclophosphamide Bortezomib Dexamthasone; IMWG: International Myeloma Working Group; ISS: International Staging System; LDH: Lactate Dehydrogenase; MR: Minor Response; NDMM: Newly Diagnosed Multiple Myeloma; OR: Odds Ratio; ORR: Overall Response Rate; OS: Overall Survival; PD: Progressive Disease; PFS: Progression Free Survivals; PR: Partial Response; RVD: Lenalidomide-Bortezomib-Dexamethasone; SAE: Serious Adverse Event; SD: Stable Disease; TD: Thalidomide-Dexamethasone; VCD: Bortezomib, Cyclophosphamide, Dexamethasone; VGPR: Very Good Partial Response; VMP: Velcade-Melphalan-Prednisolone; VMPT: Velcade-Melphalan-Prednisolone-Thalidomide; VTD: Bortezomib, Thalidomide, Dexamethasone; VTE: Venous Thromboembolism

## Introduction

Treatment for Newly Diagnosed Multiple Myeloma (NDMM) in transplant-eligible patients involves induction chemotherapy followed by high dose therapy with an Autologous Stem Cell Transplant (ASCT). This may be followed by consolidation or maintenance therapy depending upon funding and approval.

A number of first-line induction regimes exist. Bortezomib (Velcade®) based induction regimes have been found to achieve higher response rates with favourable long-term outcomes such as overall (OS) and Progression Free Survival (PFS) [1]. Of the Bortezomib based regimes, the VTD (Bortezomib, Thalidomide, Dexamethasone) triplet has gained much popularity, demonstrating higher response rates than Bortezomib combined with an alkylating agent such as Cyclophosphamide [2]. NICE currently recommend Bortezomib in combination with Dexamethasone or Dexamethasone and Thalidomide as induction therapy for NDMM prior to ASCT [3].

The current recommended dosing protocol according to the Summary of Product Characteristics entails administration of Bortezomib on a twice weekly basis [4]. However, multiple adverse effects are associated with its use, for example, neuropathy, haematological cytopenias and increased infection risk due to




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immunosuppression.

Peripheral neuropathy is the most notable side effect. It is estimated to affect approximately one third of patients with NDMM treated with Bortezomib [5], although estimates vary widely. In the GIEMMA trial comparing VTD to TD, peripheral neuropathy grade >3 developed in 10% of those on VTD after three cycles, significantly higher than the TD arm [6]. Similarly, in the PETHEMA trial, peripheral neuropathy grade >3 developed in 14% of participants follow six cycles of VTD, once again significantly higher than the TD arm [7].

Baseline characteristics associated with an increased risk include pre-existing peripheral neuropathy, diabetes mellitus and alcohol dependency. Incidence is associated with treatment regimen and cumulative dosing and is more common with intravenous than subcutaneous administration [8]. Incidence also varies with concomitant chemotherapy agents, with higher rates seen in VTD compared to VCD (Bortezomib, Cyclophosphamide, Dexamethasone) [2]. Symptoms are usually predominantly sensory with painful paraesthesia and may also have a motor component. Onset can have significant impacts on quality of life, even at lower grades, and has been demonstrated to be fatal in extreme cases [9]. It has been shown to be reversible on discontinuation of treatment in the majority of patients, however time to reverse can vary from months to years [5,10].

Moreover, autonomic neuropathy has been widely reported with Bortezomib use. This usually manifests as orthostatic hypotension resulting in dizziness and falls. Severe cases have been reported [11]. Management involves lifestyle advice and hydration and reducing other antihypertensive medication and mineralocorticoids or sympathomimetics can also be prescribed [4].

Management of Bortezomib induced neuropathy is limited to dose reduction or discontinuation following onset [12]. This may have important implications for future treatment regimes as intolerance or refractoriness to Bortezomib limits the ability to obtain Bortezomib in further treatment lines. An alternative approach that has been widely adopted involves a weekly as opposed to bi-weekly dosing interval. This is often employed in those who are older with predisposition to peripheral neuropathy as aforementioned. This dosing schedule has been widely implicated in transplant-ineligible myeloma, but to date, no clinical trials have been conducted to compare the efficacy of this dosing frequency in transplant-eligible myeloma.

## Materials and Methods

In order to investigate current Bortezomib prescribing practice locally, we conducted a retrospective audit. Real-world data was collected consecutively from all patients in our trust treated with VTD as first-line chemotherapy in the intensive treatment arm for either multiple myeloma or secretory plasmacytoma, between January 2015 and November 2020. All patients were treated at University Hospitals Leicester (UHL) a Teaching Hospital trust and tertiary Haematology center located in the East Midlands, UK.

Data was collected from electronic patient notes and chemotherapy prescription records; we collected data on VTD dosing, depth of response, side effects and Serious Adverse Events (SAE) occurring whilst on treatment, and any subsequent first-line treatment such as ASCT or maintenance chemotherapy. SAE were defined as any infection requiring hospital admission or a Venous Thromboembolism (VTE) event during the course of therapy.

Primary outcomes were depth of response to induction therapy, and the development of neuropathy (peripheral or autonomic) or SAE occurring whilst on VTD. Overall Response Rate (ORR) was defined as the proportion of patients achieving Partial Response (PR) or above. Secondary outcomes included cumulative Bortezomib dose, number of Bortezomib cycles and Thalidomide tolerance.

The twice weekly VTD regime involved Bortezomib 1.3mg/$m^2$ (maximum 2.75mg) delivered subcutaneously (SC) on days 1, 4, 8 and 11 of a 21-day cycle. In the once weekly regime, patients received the same dose of Bortezomib on days 1, 8, 15 and 22 of a 35-day cycle. Hence number of Bortezomib doses and total Bortezomib dose received in each cycle was equivalent in the two regimes. In addition, 20mg oral Dexamethasone was given the day of and day after Bortezomib doses along with 100mg oral Thalidomide each day. Patients received antimicrobial prophylaxis according to local guidelines as well as intravenous bisphosphonates as standard practice of care. Whilst on thalidomide patient were anticoagulated with Aspirin 75mg OD up to 2016, then changed to prophylactic low-molecular-weight heparin and later to DOACs in accordance to evolving local practice and guidelines.

Treatment response was assessed after completion of 4-6 chemotherapy cycles; at this point those who had achieved PR or above and who were <72 years old were assessed for ASCT. Patients were either initially commenced on weekly VTD or converted to the weekly regime when Bortezomib related side-effects became intolerable. Bortezomib prescription was at the discretion of the consultant haematologist.

Those deemed suitable underwent harvesting with 3000mg/$m^2$ Cyclophosphamide followed by myeloablative chemotherapy with Melphalan 140mg/$m^2$ or 200mg/$m^2$ with ASCT. Transplant suitability and Melphalan dosing decisions were at the discretion of the transplant consultant. Those unsuitable for transplant were offered further VD (Bortezomib and Dexamethasone) up to a maximum of 13 cycles.

Treatment response was categorized according to response of serum paraprotein levels, or serum free light chains (SFLC) in those with light chain disease, according to the International Myeloma Working Group (IMWG) uniform response criteria [13]. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5 [14].

Statistical analysis was performed on SPSS Version 26. Comparisons of baseline characteristics of continuous variables was assessed by independent sample t-test where the variable was normally distributed, or Mann-Whitney-U test where distribution did not meet the assumption of normality. For categorial baseline characteristics chi-squared ($\chi 2$) was used or Fisher's exact test where the assumptions of $\chi^2$ were not met. Comparison of continuous outcomes between groups was performed using two-sample independent t-test. Categorical outcomes were assessed by univariate logistic regression. p-values <0.05 were considered significant.

## Results

74 patients underwent VTD chemotherapy between January 2015 and November 2020. 51 patients initially commenced bi-weekly Bortezomib, 34 (66.7%) of which were converted to the weekly regime during the course of their treatment. 23 patients were initially commenced on weekly Bortezomib, two of which were stepped up to bi-weekly regime, one of who was then stepped back down to weekly regime. The total number of VTD cycles received ranged between 3 and 14. The treatment course of the cohort are set out in the flow chart (Figure 1).

15 patients (bi-weekly: 11, weekly: 5) continued maintenance chemotherapy after completing VTD induction, according to funding and approval. Since March 2021, NICE have recommended maintenance with Lenalidomide following autologous stem cell transplant in NDMM [15]. This was not approved for practice at the time many of our patients completed induction chemotherapy.

### Baseline characteristics

The baseline characteristics of the sample according to initial Bortezomib dosing frequency are shown in Table 1. Those in the weekly Bortezomib group were significantly older with a median

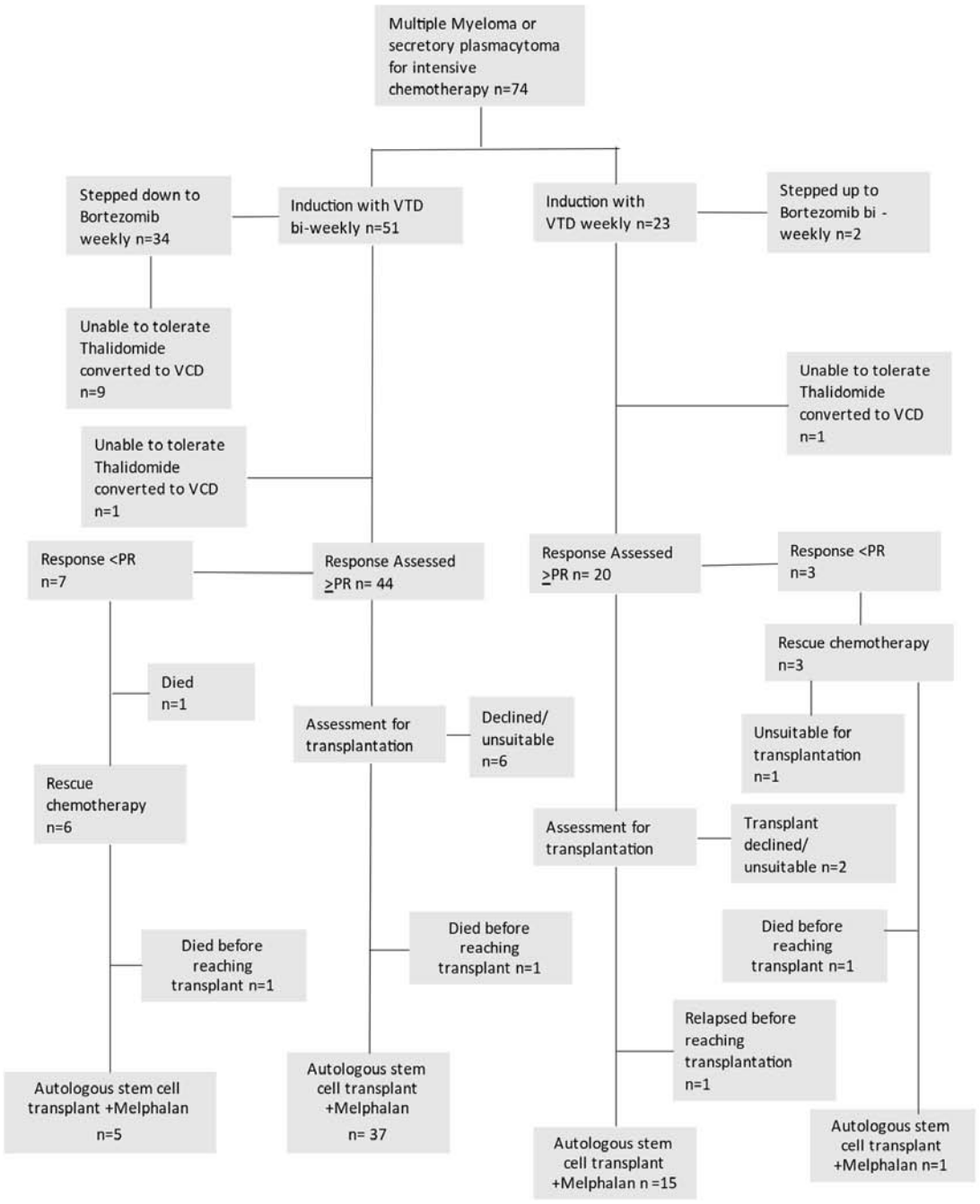


**Figure 1:** Flow chart to show treatments received and overall response of the cohort.

**Table 1:** Baseline Characteristics.

| | Bi-weekly | Weekly | p-value |
|---|---|---|---|
| n | 51 | 23 | |
| **Sex** | | | |
| Male n (%) | 31 (60.8%) | 13 (56.5%) | 0.73 |
| **Age** | | | |
| Median (range) (*) | 59 (41-75) | 69 (39-75) | <0.001 |
| **Diagnosis** | | | |
| Multiple Myeloma | 38 (74.5%) | 20 (87%) | 0.347 |
| Secretory plasmacytoma | 11 (21.6%) | 3 (13%) | |
| Unknown | 2 (3.9%) | 0 | |
| **ISS** | | | |
| 1 | 23 (45.1%) | 11 (47.8%) | 0.875 |
| 2 | 17 (33%) | 6 (26.1%) | |
| 3 | 11 (21.6%) | 5 (21.7%) | |
| Unknown | 0 | 1 (4.3%) | |
| **Paraprotein (**)** | | | |
| κ light chain | 10 (19.6%) | 1 (4.3%) | 0.034 |
| λ light cain | 1 (2%) | 4 (17.4%) | |
| IgG κ | 24 (47.1%) | 11 (47.8%) | |
| IgG λ | 15.7% (8) | 26.1% (6) | |
| IgA κ | 6 (11.8%) | 0 | |
| IgA λ | 1 (2%) | 0 | |
| Biclonal gammopathy | 1 (2%) | 1 (4.3%) | |
| **Cytogenetics** | | | |
| High risk | 15 (29.4%) | 6 (26.1%) | 0.598 |
| Standard risk | 18 (35.3%) | 10 (43.5%) | |
| Not performed | 18 (35.3%) | 7 (30.4%) | |
| **Haemoglobin (g/l):** mean (range) | 106.3 (69-147) | 113.3 (77-143) | 0.085 |
| **LDH (U/l):** mean (range) | 216 (88-462) | 247 (136-636) | 0.329 |
| **Albumin (g/l):** mean (range) | 36.2 (19-51) | 38.2 (27-50) | 0.237 |
| **Beta-2-microglobulin:** mean (range) (*) | 4.2 (1.4-20) | 3.7 (1.8-7.2) | 0.915 |
| **Calcium (mmol/l):** mean (range) | 2.6 (2.08-4.68) | 2.39 (1.76-3.04) | 0.205 |
| **Co-morbid type II Diabetes Mellitus** | | | |
| Non-diabetic | 45 (88.2%) | 20 (87%) | 0.701 |
| Diet controlled | 1 (2%) | 0 | |
| One tablet | 1 (2%) | 1 (4.3%) | |
| Two tablets | 1 (2%) | 2 (8.7%) | |
| Insulin | 2 (3.9%) | 0 | |
| Unknown | 1 (2%) | 0 | |

Baseline characteristics of cohort. Statistical analysis from independent sample *t*-test (parametric) or Mann-Whitney-U test (*) (non-parametric) for continuous variables and chi-squared analysis or Fisher's exact test (**) for categorical variables. ISS: International Staging System (IMF); LDH: Lactate Dehydrogenase.

age of 10 years greater than those in the bi-weekly group. Beta-2-microglobulin levels were also significantly higher in the bi-weekly group, although this did not give rise to any significant difference in IMF International Staging System (ISS) prognostication scores, which incorporates beta-2-microglobulin levels [16]. Paraproteins were found to have a statistically significant difference between the two groups, most likely due to the absence of IgA paraproteins in the weekly group. However, the percentage of patients with light chain disease were similar in the two groups.

**Table 2:** Transplantation.

| | Bi-weekly (n=51) | Weekly (n=23) |
|---|---|---|
| ASCT | 42 (80.4%) | 16 (69.6%) |
| Melphalan 140mg/m$^2$ | 14 (33.3%) | 11 (68.8%) |
| Melphalan 200mg/m$^2$ | 28 (66.7%) | 5 (31.3%) |
| No transplant | 9 (17.6%) | 7 (30.4%) |
| Declined | 5 (9.8%) | 2 (8.7%) |
| Unsuitable | 2 (3.9%) | 3 (13%) |
| Died/relapsed before transplantation | 2 (5.9%) | 2 (8.7%) |

Autologous Stem Cell transplant (ASCT) outcomes and high dose chemotherapy doses following VTD ((Bortezomib, Thalidomide, Dexamethasone) induction according to Bortezomib frequency.

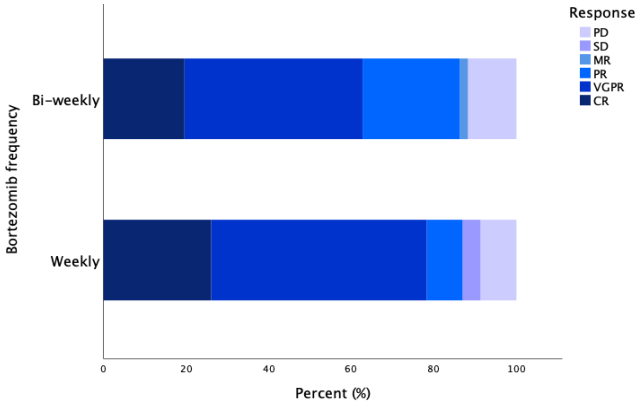


**Figure 2:** Stacked bar chart to show initial response to induction chemotherapy.

Cytogenetic testing was performed in 49 patients. High risk cytogenetics was defined as the presence of one of five high risk mutations on bone marrow aspirate testing (amp1q21, del17p13, t(4;14), t(14;16) or t(14;20)) and were present in 42.9% (21) of those tested; standard risk cytogenetics was defined as absence of these high risk mutations on cytogenetic testing and was present in the remaining 57.1% (28). (Bi-weekly: 21.6%, weekly: 21.7%). No other baseline characteristics were found to be statistically significant. Cytogenetic testing performed varies in different centers across the country, and at present neither cytogenetics or paraprotein type influences treatment recommendations in national or international guidelines.

The prevalence of diabetes mellitus in the cohort was 11% with no difference between the groups despite the age discrepancy. In the bi-weekly group one patient was reported to drink 25 units of alcohol a week and one other patient was reported to have a history of alcohol dependency.

## Stem cell transplantation

Out of the 74 patients in the cohort 58 (78.4%) underwent ASCT following induction. A higher percentage of patients in the bi-weekly group reached transplantation, with the higher Melphalan dose used

**Table 3:** Total Bortezomib received.

| Transplantation | Bortezomib frequency | n | Total Bortezomib dose (mean ± SD) | *p*-value | Number of VTD cycles (mean ± SD) | *p*-value |
|---|---|---|---|---|---|---|
| ASCT | Bi-weekly | 36 | 28.6 ± 9.94 | 0.77 | 5.64 ± 2.14 | 0.69 |
| | Weekly | 15 | 27.7 ± 6.4 | | 5.4 ± 1.12 | |
| Transplant unsuitable | Bi-weekly | 8 | 35.5± 12.3 | 0.078 | 6.63 ± 1.77 | 0.044 |
| | Weekly | 5 | 54.8 ± 23.9 | | 10.6 ± 4.5 | |

Total Bortezomib dose per unit body surface area (mg/m$^2$) and number of VTD (Bortezomib, Thalidomide, Dexamethasone) received as part of induction chemotherapy according to Bortezomib frequency and ASCT (autologous stem cell transplant) suitability. Statistical analysis from independent two-sample independent *t*-test comparing means.

**Table 4:** Response.

| | Bi-weekly (n=51) | Weekly (n=23) | OR | 95% CI | p-value |
|---|---|---|---|---|---|
| **Response** | | | | | |
| CR | 10 (19.6%) | 6 (26.1%) | 0.69 | 0.22-2.2 | 0.532 |
| VGPR | 21 (41.1%) | 12 (52.2%) | | | |
| PR | 13 (25.5%) | 2 (8.7%) | | | |
| MR | 1 (2%) | 0 | | | |
| SD | 0 | 1 (4.3%) | | | |
| PD | 6 (11.8%) | 2 (8.7%) | | | |
| **Overall response** | | | | | |
| ORR | 44 (86.3%) | 20 (87%) | 0.94 | 0.22-4.03 | 0.937 |
| ≥VGPR | 31 (60.8%) | 18 (78.3%) | 0.47 | 0.15-1.5 | 0.147 |

Initial response to VTD ((Bortezomib, Thalidomide, Dexamethasone)) induction chemotherapy by Bortezomib frequency according to the International Myeloma Working Group (IMWG) uniform response criteria. ORR (overall response rate) defined as achieving PR or above. Statistical analysis from univariate logistic regression. CR: Complete Response; VGPR: Very Good Partial Response; PR: Partial Response; MR: Minor Response; SD: Stable Disease; PD: Progressive Disease; OR: Odds Ratio; CI: Confidence Intervals.

**Table 5:** Thalidomide tolerance.

| | Bi-weekly (n=49) | Weekly (n=23) | OR | 95% CI | p-value |
|---|---|---|---|---|---|
| Well tolerated | 21 (42.9%) | 12 (52.2%) | | | |
| Dose reduction | 18 (36.7%) | 9 (39.1%) | 1.58 | 0.58-4.29 | 0.367 |
| Converted to VCD | 10 (20.4%) | 2 (8.7%) | 2.69 | 0.54-13.4 | 0.227 |

Thalidomide intolerance whilst on VTD (Bortezomib, Thalidomide, Dexamethasone) induction according to Bortezomib frequency. VCD: Bortezomib, Cyclophosphamide, Dexamethasone; OR: Odds Ratio; CI: Confidence Intervals. Significance testing from univariate logistic regression.

more frequently in this group (Table 2).

One patient underwent tandem ASCT after achieving a PR with biweekly VTD and maintenance Lenalidomide and another patient is currently being worked up for tandem ASCT. One patient underwent an allogenic SCT after ASCT, they had initially achieved only MR with biweekly VTD induction which had been followed by rescue CRd (Lenalidomide, Dexamethasone and Cyclophosphamide).

## Total Bortezomib dose

The number of Bortezomib cycles and total Bortezomib dose received during induction chemotherapy were compared between the two groups (Table 3). Patients were analysed according to their intent for transplant. Those who were refractory or progressed on VTD and required rescue chemotherapy were excluded from this analysis.

Patients receiving Bortezomib weekly received a greater number of Bortezomib cycles and larger total Bortezomib dose per unit BSA. This was much more evident in those unsuitable for transplantation. Patients unsuitable for transplantation and receiving weekly Bortezomib, received a significantly higher number of VTD cycles as shown in Table 3.

## Response

The ORR of the cohort as a whole was 87.8% with 67.6% achieving VGPR or above. The ORR according to Bortezomib frequency are shown in Table 4 and Figure 1. One patient had a pauci-secretory plasmacytoma with kappa free light chains that returned to normal limits with steroids alone and response to treatment was assessed by imaging.

ORR were very similar between the two groups. A higher proportion of those in the weekly Bortezomib groups achieved VGPR or above, but this was not found to be statistically significant.

In total, 10 patients (13.5%) in the cohort did not achieve PR after VTD. Of these, nine underwent rescue chemotherapy with a second chemotherapy regime and one died before further treatment could be initiated. Six of these patients underwent ASCT after rescue chemotherapy, two were not suitable, and one died awaiting transplantation (Figure 1).

## Thalidomide tolerance

Side effects associated with Thalidomide include constipation, oedema, rash, fatigue and dizziness. When these became intolerable,

**Table 6:** Adverse effects and serious adverse events.

| | Bi-weekly (n=49) | Weekly (n=23) | Odds Ratio | 95% CI | p-value |
|---|---|---|---|---|---|
| **Peripheral Neuropathy** | | | | | |
| Peripheral Neuropathy (any grade) | 31 (63.3%) | 12 (52.2%) | 1.58 | 0.58-4.31 | 0.372 |
| Peripheral Neuropathy grade ≥ 2 | 10 (19.6%) | 2 (8.7%) | 2.7 | 0.54-13.4 | 0.227 |
| **Autonomic Neuropathy** | | | | | |
| Autonomic Neuropathy (any grade) | 13 (26.5%) | 2 (8.7%) | 3.79 | 0.78-18.5 | 0.099 |
| Autonomic Neuropathy grade ≥2 | | | | | |
| Autonomic Neuropathy grade ≥3 | 3 (6.1%) | 0 | - | - | 0.546 |
| **Haematological** | | | | | |
| Any | 2 (4.1%) | 1 (4.3%) | 0.9 | 0.08-10.43 | 0.931 |
| Anaemia | 0 | 0 | | | |
| Neutropenia | 1 (2%) | 0 | | | |
| Thrombocytopenia | 1 (2%) | 1 (4.3%) | | | |
| **Other** | | | | | |
| Chemical conjunctivitis | 2 (4.1%) | 0 | - | - | |
| Tinnitus | 1 (2%) | 0 | - | - | |
| Sensorineural hearing loss | 1 (2%) | 0 | - | - | |
| Acute pancreatitis | 1 (2%) | 0 | - | - | |
| **Hospital Admissions** | | | | | |
| ≥1 | 33.3% (17) | 11 (47.8%) | 0.55 | 0.2-1.49 | 0.237 |
| ≥2 | 12% (6) | 3 (13%) | 0.89 | 0.02-3.92 | 0.876 |
| 3 | 5.9% (3) | 0 | - | - | 0.548 |
| **VTE** | | | | | |
| Any VTE | 1 (2%) | 3 (13%) | 0.13 | 0.01-1.35 | 0.089 |
| DVT | 0 | 3 (13%) | - | - | |
| PE | 0 | 0 | - | - | |
| SVT | 1 (2%) | 0 | - | - | |
| **Arterial Thrombosis** | | | | | |
| Any | 1 (2%) | 0 | - | - | |
| Stroke | 1 (2%) | 0 | - | - | |

Adverse effects, thrombotic events and infections requiring hospital admission whilst on VTD (Bortezomib, Thalidomide, Dexamethasone) intensive induction chemotherapy according to Bortezomib frequency. Side effects graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Statistical analysis from univariate logistic regression or Fisher's exact test (*). DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; SVT: Superficial Vein Thrombosis; CI: Confidence Intervals.

Thalidomide dose was reduced from 100mg to 50mg. Patients unable to tolerate Thalidomide were substituted with Cyclophosphamide 350mg/m$^2$ OD PO (VCD). 12 patients (16.2%) in the cohort required conversion to the VCD regime. Table 5 shows Thalidomide intolerance according to Bortezomib dosing frequency. There was a trend of improved Thalidomide tolerance in those on weekly Bortezomib, demonstrated by fewer patients requiring a dose reduction or conversion to VCD.

## Adverse effects and serious adverse events

The commonest side effects seen were neuropathy (peripheral and/or autonomic) (Table 6) as previously reported with Bortezomib use. Both peripheral and autonomic neuropathy were more common in with bi-weekly Bortezomib, particularly at higher grades (Table 6). On development of grade 2 peripheral neuropathy, patients on the bi-weekly regime were converted to the weekly regime, where no patients progressed to grade 3.

Aside from neuropathies, haematological cytopenias were also reported. One grade 4 adverse effect occurred; a case of pancreatitis attributed to Bortezomi in a patient on the bi-weekly regime. (Table 6). No adverse effects other than neuropathies or haematological cytopenias were seen in those in the weekly group. Other side effects seen whilst on bi-weekly dosing were chemical conjunctivitis (grade 2), tinnitus (grade 1) and sensorineural hearing loss (grade 1). No patients died whilst on VTD induction. Information on side effects was unavailable in two patients.

Venous Thromboembolism (VTE) is a well-recognized adverse event with chemotherapy treatment due to their procoagulant effect. This is more closely associated with Thalidomide than Bortezomib. The adjuvant prophylactic anticoagulation recommended whilst on the VTD regime varied within the time frame of data collection.

Thrombotic events in our cohort whilst on VTD were relatively rare. Three patients were diagnosed with Deep Vein Thromboses (DVTs) whilst on the weekly regime, all of which were on prophylactic Dalteparin at the time. There was one case of a superficial vein thrombosis at the left antecubital fossa, occurring in a patient on weekly Bortezomib (initially commenced on bi-weekly) and whilst on Apixaban. No cases of pulmonary embolism were seen. Arterial thrombotic events were relatively rare within the cohort, with one patient suffering a stroke whilst not anticoagulated (Table 6).

## Discussion

A number of induction regimes for NDMM exist. VTD is currently recommend nationally, and is one of the most common regimes used internationally especially when lenalidomide is not funded [12]. Induction aims to achieve the highest possible response, with deeper responses associated with better long-term outcomes [17,18]. However, intensive chemotherapy must be counterbalanced with the risk of drug related toxicities.

Intolerance to bi-weekly Bortezomib is common and widely reported. Peripheral neuropathy is the most significant dose limiting adverse event, seen in approximately one-third of patients [5]. Despite its frequency, there are no current guidelines on Bortezomib dosing amendments following the development of neurotoxicity. Practice varies with alternatives including dose reduction, altering dose frequency or discontinuation. A number of alternative dosing regimens have been adopted, with no current agreed consensus.

Locally, we have adopted a weekly dosing regimen either initially or following the onset of side effects. Our alternative dosing regimen consists of the same dosing strength and number of doses, delivering the same total Bortezomib dose per cycle.

Here we provide evidence that this alternative regime is not associated with worse outcomes in terms of response to induction chemotherapy, with an almost identical ORR (>PR) and higher percentage of patients achieving >VGPR and CR. This regime was better tolerated with lower rates of peripheral and autonomic neuropathy, particularly at higher grades, despite this group being significantly older. In addition, hospital attendance is required for Bortezomib administration and we anecdotally report that wider spacing is more convenient and preferred by patients in terms of hospital visitation. Long-term outcomes were not investigated, however, given the correlation between deeper initial response and better long-term prognosis, we expect this to have no adverse impact on long-term outcomes. Achieving deeper responses with induction therapy has been shown to be favourable for long-term prognosis [12,19], and we saw a higher percentage of patients in the weekly group achieving >VGPR and CR. Overall our therapeutic responses appear similar to published outcomes with VTD induction for NDMM [20-22].

Only 17 of the 51 (33.3%) patients started on bi-weekly Bortezomib were able to tolerate the twice weekly dosing frequency for the duration of their induction chemotherapy. The true tolerance rate of this regime is likely to be lower than this as patients felt to be at higher risk of side effects were commenced on weekly Bortezomib from the outset.

Following onset of neuropathy, patients in the bi-weekly regime were converted to the weekly regime. This will have prevented progression to higher grades adverse effects (in particular peripheral neuropathy) and development of further side effects, leading to opposing plausible residual confounding. Hence the true incidence and severeness of the adverse effect profile of the bi-weekly regime is likely much greater than presented above. By this means, no patients developed peripheral neuropathy higher than grade 2 and no patients required Bortezomib dose reduction. In a similar fashion, the approach of starting on bi-weekly Bortezomib and electively converting to a weekly dosing in later cycles has been employed clinical trials. For example, the ALCYONE trial used bi-weekly Bortezomib for cycles 1-2 followed by weekly Bortezomib for cycles 3-9 for transplant-ineligible NDMM [23].

In our cohort, the only Grade 4 adverse effect seen was a case of acute pancreatitis whilst on the bi-weekly regime. Acute pancreatitis related to Bortezomib use has been previously reported [24].

Multiple myeloma is associated with an increased risk of VTE, which is increased further when on chemotherapy treatment. It is interesting to note that VTE events were only seen in those on weekly Bortezomib despite concurrent prophylactic heparin. This may in part have been influenced by better Thalidomide tolerance, as well as the fact that this group were significantly older. The low rate of VTE events makes this difficult to analyses. Adjuvant anticoagulation prescriptions changed during the course of this study, and VTE events are likely to be prevented in future by the use of a DOACs alongside Thalidomide.

To date, no clinical trials have investigated the efficiency of weekly Bortezomib in transplant-eligible patients. In current clinical practice, patients are commenced on bi-weekly dosing and prescriptions are altered after onset of adverse effects. Here we present data from patients who were commenced on the weekly regime from the onset. We believe this approach may be an appropriate recommendation in the future, either as a standard or for select patient groups.

An alternative cause of action following onset of neuropathy is a dose reduction to 1mg/m$^2$ or 0.7mg/m$^2$ [12]. Outcomes of initial therapeutic response for trials adopting this dose reduction appear unfavourable [21] compared with those adopting weekly dosing regime [20] and the data presented above, although as far as we are aware this has never been formally investigated. We believe the weekly dosing interval provides an option for reduced toxicities without compensating treatment effectiveness.

Much of the pathophysiology of Bortezomib induced neurotoxicity remain to be determined. Here, lower rates of neuropathy were seen with weekly dosing despite a higher total Bortezomib dose. This suggests toxicity is not only related to total cumulative dose, but the time period over which doses are given. Bortezomib neuropathy is reported to develop at a cumulative dose of 30mg/m$^2$ [5]. This was roughly equivalent to the cumulative dose both groups received prior to ASCT. However, in those not suitable for transplantation, those receiving Bortezomib weekly were able to tolerate much higher doses than this, although the small sample size of this group limits this analysis (Table 4). This greater cumulative dose tolerance has been seen in other reports of weekly Bortezomib dosing, for example, Miguel et al. report the tolerance of an average of 8 cycles of Bortezomib with Melphalan in transplant-ineligible NDMM through converting from

bi-weekly to weekly dosing after cycle 4 [25]. Tolerance of higher total doses of induction chemotherapy has particular relevance in this group, as without consolidation with transplantation they rely on induction chemotherapy alone to achieve and maintain their first remission.

Weekly Bortezomib has been widely implemented in transplant-ineligible NDMM. Mateos et al. use evidence from the VISTA, GIMEMA and ALCYONE demonstrate that in the VMP (Bortezomib, Melphalan, Prednisolone) regime, weekly dosing of Bortezomib significantly reduces peripheral neuropathy without impacting on median PFS, advocating this dosing schedule for this patient cohort [26]. The GIMEMA study comparing VMP with VMPT (Bortezomib-Melphalan-Prednisone plus Thalidomide) in transplant-ineligible NDMM required a protocol amendment during the course of the study from bi-weekly to weekly Bortezomib [27]. Post-hoc analysis showed the weekly regime was associated with significant lower incidence of peripheral neuropathy with comparable efficacy. They report higher compliance rates with fewer patients discontinuing treatment or requiring dose reduction [28]. Other examples include the RVD lite regime [29] with the Lenalidomide-Bortezomib-Dexamethasone triplet.

The use of the weekly regime in transplant-eligible NDMM is much less established, but has been reported in a range of settings. Reeder et al. 2010 investigated the use of weekly Bortezomib in a regime with Cyclophosphamide and Dexamethasone (CyBorD). They compared the standard bi-weekly regime with weekly Bortezomib at a higher dose (1.3 mg/m2 Bortezomib days 1, 4, 8 and 11 compared with 1.5mg/m$^2$ Bortezomib days 1, 8, 15 and 22). They report that this wider dosing interval enabled toleration of higher dose with no increase in the incidence of peripheral neuropathy and fewer SAE, whilst achieving a similar ORR [30].

Once weekly intravenously Bortezomib has also been reported by Yoa et al. through retrospective data analysis of patients treated in two hospitals in China. Their once weekly treatment arm received Bortezomib at a higher dose of 1.6mg/m$^2$ but on only three days (Day 1, 8, and 15) of a 28-day cycles compared to the standard bi-weekly regime. They demonstrated that this regime achieved similar ORR and PFS but with lower incidence of therapy induced thrombocytopenia [31].

The use of real-world data means patients were not randomised or systematically assigned to their initial dosing frequency. This was determined by the prescribing consultant Haematologist assessing the patient at the time of the initial prescription, influenced by patient factors, with subjective variance between clinicians. This is likely to have influenced the heterogeneity between the groups, in particular with age.

Another limitation of this study is that, following the onset of adverse effects or SAE, patients on the bi-weekly regime were converted to the weekly regime to facilitate tolerance. This may well have averted worsening of side effects. This is likely to decrease the severity of the side effects profile in the bi-weekly group and making differences between the two groups more subtle. The high rate of patients starting on the bi-weekly regime being converted to the weekly regime during their treatment course may well reflect the difficultly in tolerating the bi-weekly regime. Nonetheless, this is difficult to interpret as the decision to convert to a different dosing frequency was a clinical decision made during the consultation and was also influenced by patient clinician's preferences. Wide variations in post induction treatment inhibited long-term survival outcome analysis as groups were non-comparable; this difference is likely due to the age difference between the two groups with a higher proportion of those in the bi-weekly group undergoing ASCT and with the higher Melphalan dose (200mg/m2) used more often (Table 2).

To conclude, we describe the use of weekly SC Bortezomib with equivalent dosing strength and quantity but with wider dosing intervals as part of the VTD induction for NDMM. This is an approach that has been adopted locally to overcome the dose limiting peripheral neuropathy associated with Bortezomib. We provide real-world data to show that this is better tolerated and equally efficacious efficient in terms of initial therapeutic response. We propose that this can be utilized as an alternate regime in patient intolerant to bi-weekly Bortezomib or eventually adopted as a standard. Once weekly Bortezomib dosing could be further investigated by a prospective randomised control trial to better determine efficacy and long-term outcomes.

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