Prevention of Bortezomib-Induced Polyneuropathy in Multiple Myeloma Patients

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Abstract: Bortezomib (Velcade®) is a proteasome pathway inhibitor that has improved multiple myeloma (MM) overall survival. Bortezomib-induced peripheral neuropathy (BIPN) is a frequent adverse event, requiring delay, dose reduction or cessation of therapy. Although most of the symptoms resolve after discontinuation or dose-reduction, almost 25% develop chronic symptoms, affecting quality of life and limiting the therapeutic choices.

There is limited evidence regarding the strategies to prevent bortezomib-induced polyneuropathy (BIPN). We conducted a review of the published data to summarize the available information regarding BIPN prevention strategies.

Our search included literature published in the Cochrane Library databases, Medline/PubMed, SciELO, Google Scholar, and Trip Database in the last ten years, including observational analytic studies, experimental studies, systematic reviews, and metanalysis, which reported the efficacy of interventions to prevent BIPN.

Eight studies have been included. The subcutaneous administration of bortezomib has shown a protective effect of all grades of BIPN (OR=0.40, 95% CI 0.27 to 0.59, p<0.001) and grade 3 to 4 (OR = 0.45, 95% CI 0.25 to 0.82, P<0.05), as evidenced in a metanalysis. Cumulative dose of bortezomib ≥ 30 mg/m2 is significantly associated with a higher risk of BIPN.

Other therapies as Acetyl-l-carnitine (ALC), dexamethasone in partnered dosing (day of/after bortezomib), high-dose intravenous mecobalamin (HDIME), and the combination of docosahexaenoic acid, α-lipoic acid, vitamin C 60 mg, and vitamin E have been assessed but their efficacy for BIPN prevention has not been confirmed.

We conclude that the subcutaneous route of administration of bortezomib effectively prevents BIPN while other strategies lack robust evidence to be recommended.

Keywords: Bortezomib, Multiple myeloma, Peripheral neuropathy.

INTRODUCTION

Bortezomib (Velcade®) is a dipeptidyl boronic acid that selectively inhibits the ubiquitin-proteasome pathway. The drug's antineoplastic effect relies on the reversible inhibition of the mammalian 26S proteasome subunit and the interaction with the nuclear factor kappa B (NFκB) system, provoking the cytoplasmic aggregate accumulation of non-degraded proteins and the consequent cell cycle arrest [1].

This drug has improved overall survival for multiple myeloma (MM) patients, and is part of standard-of-care protocols, both in newly diagnosed and relapsed disease [1, 2]. It is also used for long-term maintenance.

Neurotoxicity is a common toxicity associated to Bortezomib. Overall incidence of all-grade BIPN has been reported in 8,4% to 80,5% and when developed, it requires dose reduction, delay or cessation of treatment. Multiple mechanisms are involved in neurotoxicity, including the nuclear retention of polyadenylated RNAs, DNA damage, and tubulin polymerization, causing the accumulation of neurofilaments in the soma, axonal transport degeneration, mitochondrial calcium influx, generation of reactive oxygen species (ROS), and apoptosis induced by caspase activation. The indirect blockage of nerve-growth-factor-mediated neuronal survival by the inhibition of NF-κB and neurotrophins dysregulation has been associated with neuropathy [3] (Figure **1**). Several clinical factors have been associated with higher risk of BIPN, including age, diabetes, cumulative dose, administration route and the use of other neurotoxic agents. Despite the evidence of reversibility after dose reduction or cessacion, it results a persistent adverse effect in more than 25% of patients [4].

Considering there are no drugs approved to prevent, attenuate or cure BIPN, prevention is essential. This review focuses on the various approaches developed for BIPN prevention.

METHODS

Searches were undertaken using the Cochrane Library databases, Medline/PubMed, SciELO, Google

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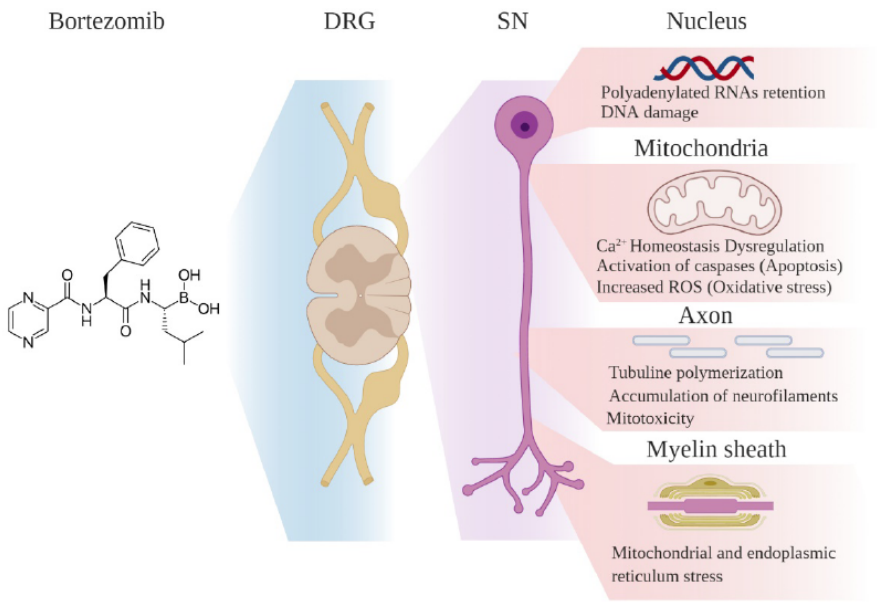

Figure 1: Mechanisms of bortezomib-induced polyneuropathy; DRG, dorsal root ganglion; SN, sensitive neuron. *Created with BioRender.com.*

Scholar, and Trip Database. For MEDLINE/PubMed search, the combination "multiple myeloma" AND "bortezomib" AND "neuropathy" AND "prevention" applying the filters, publication date (10 years), species (Humans), and article type (Clinical Trials AND Metanalysis) was used. The same terms were used in other search engines such as Scielo and Google scholar (Supplementary data). In Trip Database, we used the PICO terms; P: Multiple myeloma; I: Bortezomib; O: Neuropathy. We limited the search to studies published in the last ten years, including observational analytic studies, experimental studies, systematic reviews, and metanalysis, which reported the efficacy of interventions to prevent BIPN. We used full-text available articles and abstracts in English. The search was conducted between September and October 2020.

RESULTS

The search retrieved eight studies describing the effect of Bortezomib schedule, Bortezomib route of administration, Acetyl-l-carnitine (ALC), High-dose intravenous mecobalamin (HDIME), and the combination of docosahexaenoic acid (DHA), α -lipoic acid (ALA), vitamin C, and vitamin E, in BIPN prevention.

Bortezomib Schedule

A pooled analysis of clinical trials have described how dexamethasone schedule impacts BIPN prevention. This included 1416 patients with dexamethasone in partnered dosing (day of/after bortezomib)(days 1, 2, 4, 5, 8, 9, 11 and 12), 191 patients with dexamethasone in weekly dosing (days 1, 8, and 15), and 1090 patients in other schedules (days 1–4, 8–11, and similar). Peripheral neuropathy (PN) rates were lower in the partnered schedule (45.5%, vs. 63.9%, vs. 47.5%, respectively). Additionally, the frequency of PN grade ≥3 was lower in the partnered schedule (5.3%, vs. 11.0%, vs. 9.6%). This benefit was also reported in regimens without thalidomide (4.2%, vs. 11.0%, vs. 8.6%). The use of partnered doses of dexamethasone was associated with a reduction in the frequency of severe BIPN compared to "other" schedules, (OR 1.44; 95% CI 1.03 to 2.02; p = 0.03), while the inclusion of thalidomide was associated with an increased risk of severe PN (OR 1.62; 95% CI 1.16 to 2.26; p < 0.01). Although the studies' heterogeneity and the lack of data regarding baseline PN did not allow the authors to draw a definite conclusion, partnered dose of dexamethasone may be associated with less severe BIPN [5].

Bortezomib Route of Administration

The subcutaneous administration of bortezomib was associated with reduced BIPN in a study including 344 myeloma and amyloidosis patients, compared with other routes of administration (26.9% vs. 44.3%, p = 0.001), maintaining similar response rates (76.6% vs. 72.1%, p = 0.15). Multivariable analyses also

evidenced a higher PN risk (OR 2.45, 95% CI 1.26-4.76, p = 0.008) for other bortezomib administration schedules compared to subcutaneous and weekly [6]. A similar result was evidenced in patients receiving the combination of Bortezomib and Thalidomide, with a lower frequency of PN in patients treated with subcutaneous bortezomib compared with intravenous bortezomib (all grade PN: 51.3 vs. 61.3%, p=0.371; grade ≥2: 35.1 vs. 56.8%, p=0.052; grade ≥3: 2.7 vs. 20.5%, p=0.015, respectively), particularly in severe cases [7].

A randomized, phase 3, non-inferiority study, compared the subcutaneous and intravenous routes of bortezomib administration, in 222 patients with relapsed MM. Patients in the subcutaneous administration group had less frequency of any grade BIPN (38% vs. 53%; p=0.044), grade 2 or worse (24% vs. 41%; p=0.012), and grade 3 or worse (6% vs. 16%; p=0.026) [8]. Similar results were published in a meta-analysis that included seven randomized controlled trials and six retrospective cohort studies involving 1,198 patients. A protective effect for subcutaneous administration of bortezomib to prevent all grades of BIPN (OR=0.40, 95% CI 0.27 to 0.59, p<0.001) and grade 3 to 4 (OR = 0.45, 95% CI 0.25 to 0.82, P < 0.001), was shown, while its anti-myeloma effect was maintained [9].

Bortezomib Cumulative Dose

The SUMMIT and CREST trials reported the incidence of PN increased proportionally to the cumulative bortezomib dose, particularly when it reached 30 mg/m2, with a statistically significant correlation between the total bortezomib dose and the FACT/GOG-Ntx questionnaire (p=0.0037) and the total PN score (p<0.0001) [10].

Acetyl-l-Carnitine (ALC)

ALC, a molecule associated with a preventive effect for neuronal cell death, was evaluated in a quasi-experimental study to prevent chemotherapy-induced peripheral neuropathy in patients with relapsed or refractory MM treated with bortezomib, doxorubicin, and low-dose dexamethasone (BDD). Even when the incidence of grade ≥3 polyneuropathy was 32% in the BDD group versus 15 % in the BDD and ALC group, this study did not found a statistically significant clinical benefit of including ALC for BIPN prevention in the BDD protocol [11].

High-Dose Intravenous Mecobalamin (HDIME)

A single-center randomized clinical trial published in Chinese, with abstract in English, including 65 newly diagnosed MM receiving bortezomib, reported that the incidence of BIPN in patients receiving HDIME group was lower than the control group (29.63% vs. 55.26%, chi square=4.197, p<0.05). Additionally, grade 2 or ≥3 BIPN were lower in the HDIME group as compared with the control group (18.52% vs 47.37%, chi square=5.746, p<0.05) (3.71% vs 21.05%, chi square=3.983, p<0.05). The authors conclude that HDIME in the BIPN prophylaxis has good efficacy without severe adverse effects [12]. We found no other articles regarding HDIME for BIPN prevention.

Drug Combination

A prospective study including adult patients with newly diagnosed MM receiving bortezomib-based regimens, found that docosahexaenoic acid (DHA) 400 mg, α-lipoic acid (ALA) 600 mg, vitamin C 60 mg, and vitamin E 10 mg bid may prevent BIPN. Among the 18 patients who finished the study, eight did not experience any neurotoxicity, ten (55.5%) had mild sensory PN (grade 1 NCI-CTCAE), and none had grade 2 or higher PN, versus the 40% anticipated based on the reported literature [13].

DISCUSSION

MM is a hematological neoplasm that presents diverse clinical manifestations, which may include PN. Drugs used to treat MM, such as bortezomib or thalidomide, are associated with an increased risk of PN [14].

High-dose intensity, increased cumulative dosing levels, intravenous administration, and combination therapy with thalidomide have been associated with BIPN development in MM patients in a recent systematic review of phase III trials [15].

The most robust evidence regarding prophylactic measures to prevent BIPN supports the use of subcutaneous bortezomib, with non inferior efficacy compared to intravenous administration. Subcutaneous administration had fewer adverse events such as PN, leukopenia, and thrombocytopenia (p<0.05) [16], while no differences in 1-year OS and 1-year PFS were found (p>0.05).

Methylcobalamin (MeCbl) is a form of vitamin B12 needed for the normal nervous system's functioning. Its

deficiency causes neuropathy. MeCbl is used to treat diabetic PN and other nervous disorders, including Alzheimer's disease. It significantly improves *de novo* DNA methylation, modulating the nociceptive sensitization in rats [17]. We found only one study demonstrating promising results of MeCbl to prevent BIPN. The level of evidence is too low to include MeCbl as a recommended agent.

The combination of DHA, ALA, vitamin C, and vitamin E has been reported to prevent BIPN in MM. However, similarly to MeCbl, the evidence to support its use is limited.

An update of the American Society of Clinical Oncology (ASCO) guidelines on the Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers did not found strong evidence to recommend HDIME, DHA, ALA, Vitamin C, or vitamin E in the prevention of neuropathy associated with chemotherapeutic drugs including vincristine, oxaliplatin, and taxanes [18].

Conclusion: in this review, we conclude that the subcutaneous route of administration of bortezomib effectively prevents BIPN, with a benefit that extends to protocols that include other neurotoxic agents. Other preventive strategies lack robust evidence to be recommended.

SUPPLEMENTARY MATERIAL 1

PubMed searching link

https://pubmed.ncbi.nlm.nih.gov/?term=%22multiple+myeloma%22+AND+%22bortezomib%22+AND+%22neuropathy%22+AND+%22prevention%22&filter=pubt.clinicaltrial&filter=pubt.meta-analysis&filter=datesearch.y_10&filter=hum_ani.humans

Trip Database searching link

https://www.tripdatabase.com/search?criteria=(title%3amultiple+myeloma)(title%3abortezomib)(title%3aneuropathy)

Google scholar searching link

https://scholar.google.com/scholar?start=0&q=bortezomib+induced+peripheral+neuropathy+prevention&hl=es&as_sdt=0,5&as_ylo=2010&as_yhi=2020

SciELO searching link

https://search.scielo.org/?q=bortezomib+induced+neuropathy&lang=es&count=15&from=0&output=site&sort=&format=summary&fb=&page=1&q=bortezomib+neuropathy&lang=es&page=1

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