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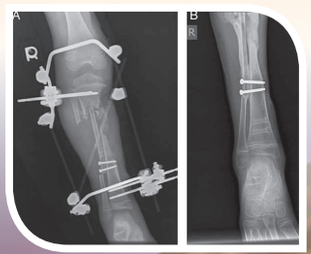

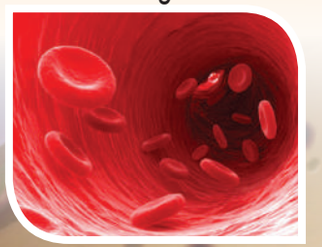

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Vitamin K2-7, a Promising Solution to Peripheral Neuropathy aroused due to Multiple Myeloma Treatment

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Abstract

Objective: **A large number of patients with Multiple Myeloma (MM) develop Peripheral Neuropathy (PN). This is either consequent upon iatrogeny with prolonged therapy or as a part of the disease. The persistence of disabling PN, during therapy, often compels the physician to a reduction in the dose of the primary agents or their total discontinuation or replacement. Our previous study with Vitamin K2-7 has shown therapeutic activity in patients with diabetic neuropathy and/or with vitamin B12 deficiency. An anecdotal observation of considerable relief of PN in an MM patient, after chemotherapy, prompted us for this observational study. The present brief communication reports the ameliorative potential of Vitamin K2-7 in the management of iatrogenic PN in MM.**

Material and Methods: **This communication describes a case-series of seventeen patients with iatrogenic PN for MM. Vitamin K2-7 was given orally to patients who complained of PN till 4 chemotherapy cycles and followed up to 5th chemotherapy cycle. Symptoms included tingling, numbness along with burning sensation, fatigue and cramps. This study was approved by an independent ethics committee.**

Results: **Twelve out of seventeen patients reported relief. Vitamin K2-7 had allowed these twelve patients continuation of treatment for MM, without any reduction of dosage or temporary discontinuation of treatment. Three patients had discontinued the MM treatment and two had discontinued Vitamin K2-7 on their own after they did not find any marked relief.**

Conclusions: **This preliminary observational study, to our knowledge, suggests for the first time that Vitamin K2-7 has an ameliorative potential for relief of iatrogenic PN in MM patients. The positive directionality of the outcome necessitates a larger study with an objective assessment of PN with Nerve Conduction Velocity and with the use of validated Visual Analog Scale for subjective features of PN.**

Keywords: **Multiple myeloma, Vitamin K2-7, Peripheral Neuropathy, Drug-induced Neuropathy.**

Conflict of Interest:

- *Dr. Dilip Mehta is CEO and Chairman of Synergia Life Sciences Pvt. Ltd.*
- *Dr. Yogesh Dound is Medical Director of Synergia Life Sciences Pvt. Ltd.*
- *Dr. Shashank Jadhav is Medical Associate of Synergia Life Sciences Pvt. Ltd.*

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Introduction

Multiple myeloma (MM) is a type of hematological cancer which is characterized by excessive production of malignant plasma cell clones in the bone marrow. Based on the biology of the plasma cells we can have the following types:

1) Active (symptomatic) MM,
2) Monoclonal gammopathy of undetermined significance,
3) Smoldering MM,
4) Asymptomatic MM and
5) Solitary plasmacytoma of bone [1].

Currently, for the management of MM, the therapy is initiated with one of the triplet drugs viz. Bortezomib-Lenalidomide-Dexamethasone (VRD), Bortezomib-Cyclophosphamide-Dexamethasone (VCD) or Bortezomib-Thalidomide-Dexamethasone (VTD) [2].

Peripheral Neuropathy (PN) is observed in 70% of patients either due to iatrogeny of prolonged treatment with drugs for MM or as a part of the disease itself [3]. Drug-induced neuropathy is a debilitating event in patients with myeloma compelling the physician to a dose reduction of the primary agents (Bortezomib, Thalidomide, Lenalidomide), or its cessation. European Myeloma Network Guidelines suggest that a reduction of PN induced by bortezomib can be achieved by: a) a prompt dose modification; b) once a week instead of twice weekly application and c) subcutaneous route rather than the commonly used intravenous administration [4].

The drugs to alleviate drug-induced neuropathy include gabapentin or pregabalin; tricyclic antidepressants such as amitriptyline, nortriptyline, and imipramine; serotonin and norepinephrine reuptake inhibitors; carbamazepine; and opioid-type analgesics [5]. The local application of lidocaine or menthol-containing analgesic cream can temporarily alleviate bortezomib-induced pain [6].

Considerable symptomatic relief in PN due to vitamin B12 deficiency and/or type 2 diabetes mellitus with Vitamin K2-7 treatment [7] prompted us to offer the therapy to patients suffering from iatrogenic PN related to chemotherapy for MM.

Material and Methods

Study Design

An open-labeled observational study was conducted to evaluate the safety and activity of Vitamin K2-7 (MK-7) in patients with MM with drug-induced PN. Approval of the study was granted by an independent ethics committee, Intersystem Bio-Medica Ethics Committee (ISBEC/NR-13/KM/VM/2015), Vile Parle, Mumbai, India. The observational study was conducted in patients who attended the Empire Haematology Oncology Day Care Centre at Bandra, Mumbai, India.

Criteria of inclusion

Patients satisfying the following inclusion and exclusion criteria were enrolled in the study. Male or female patients aged 18-65 years, suffering from drug-induced PN caused by chemotherapy received by patients of MM, who gave informed consent.

Criteria of exclusion

The following criteria of exclusion were employed: (1) Presence of any major illness other than MM, (2) a past participation by the patient in clinical trials of investigational drugs or biologics within the last 3 months, (3) patients receiving oral contraceptives, coumarin analogues and quinine, (4) patients with seropositive HIV/ HBsAg status, (6) patients with a history of alcohol, substance abuse in the last one year, and (5) pregnancy.

Primary outcomes

The primary objective of the study was to detect therapeutic activity and tolerability of Vitamin K2-7 in patients of MM, with symptoms and signs of PN.

Study procedure

Patients of MM with PN symptoms, fulfilling the criteria of selection, were enrolled after obtaining a written informed consent form (approved by ISBEC). The confidentiality of data was maintained for all the subjects throughout the study. All the demographic, anamnestic, clinical and laboratory data were recorded in a standard case record form approved by ISBEC.

A detailed history, physical examination, and essential laboratory investigations helped to select patients as per the criteria (vide supra). The chemotherapy protocols were defined. Then the patients were assessed at follow-ups at the end of each chemotherapy cycle (21 days). A detailed physical (general and systemic) examination was done both at the baseline and at every visit. The patients were given 2 capsules (100 mcg or 350 mcg each) a day of Vitamin K2-7 till the end of 4 chemotherapy cycles and followed up to the 5th chemotherapy cycle. The subjective severity of the symptoms of PN was enquired at regular follow up visits at baseline and thereafter every week till the end of the 5th cycle. The safety was assessed by clinical tolerability, side effects, and adverse events and by any change in the organ function tests. The therapeutic activity was assessed by noting the reduction in the severity of the

symptoms of PN viz. tingling and numbness along with weakness, fatigue and cramps as compared to the baseline. Any other effect during the therapy – beneficial or adverse – was also recorded.

Complete blood counts were done by standard Coulter Counter. ESR was done by Wintrobe method. Liver function tests and renal function tests were done by standard biochemical methods. Prothrombin time was done by the coagulation method.

Vitamin K2-7 was supplied by Synergia Life Sciences Pvt. Ltd., in the form of capsules (100 and 350 mcg) packed 30 capsules per bottle. The capsules were supplied in bottles to patients at the time of the enrollment and at an interval of every 15 days. Patient ingested a capsule of Vitamin K2-7 (100 mcg or 350 mcg) twice daily every morning immediately after breakfast and immediately after dinner till the end of the 4th chemotherapy cycle. The drug compliance was judged by counting the capsules in the bottle brought back at the follow-up visits. The patient was said to be compliant if he had consumed minimum 80% of the total dispensed capsules.

Results

The details of the patients who continued with Vitamin K2-7 for PN induced by the therapy for MM are outlined in Table 1. After treatment with Vitamin K2-7, the symptoms of PN reduced giving immense relief to the patients and helped them to continue their treatment without any reduction of dose or any modification. Three of the remaining five had discontinued the myeloma treatment. and two had discontinued Vitamin K2-7 on their own in a fortnight or month after they did not find any symptomatic relief in PN. Figure 1 describes the response distribution of patients, from recruitment until the end of the study.

Table 1: Details of patients of Multiple Myeloma (MM) along with treatment

Sr. No	Initials	Age M/F	MM Treatment	PN Symptoms			Effect
				T	N	B	
1	DM	55 / M	Lenalidomide, Dexamethasone	Yes	Yes	-	Complete Relief
2	AA	54 / F	Bortezomib, Cyclophosphamide, Dexamethasone	Yes	Yes	-	Complete Relief
3	AM	69 / F	Dexamethasone	Yes	Yes	-	Complete Relief
4	GQ	63 / M	Lenalidomide Dexamethasone	Yes	Yes	-	Mild Relief
5	SJ	64 / M	Lenalidomide, Dexamethasone, Zoledronic Acid	Yes	Yes	-	Complete Relief
6	SS1	57 / M	Bortezomib, Cyclophosphamide, Dexamethasone	Yes	Yes	Yes	Complete Relief
7	SS	65 / F	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone.	Yes	Yes	-	Complete Relief
8	AK	42 / F	Lenalidomide, Dexamethasone, Zolendronic Acid	Yes	Yes	-	Moderate Relief
9	SS2	85 / M	Bortezomib, Cyclophosphamide, Dexamethasone	Yes	Yes	-	Complete Relief
10	NJ	80 / M	Bortezomib, Lenalidomide, Dexamethasone	Yes	Yes	-	Moderate Relief
11	DB	70 / M	Bortezomib, Cyclophosphamide, Dexamethasone	Yes	No	-	Complete Relief
12	AN	45 / F	Bortezomib, Cyclophosphamide, Dexamethasone	No	Yes	-	Mild Relief

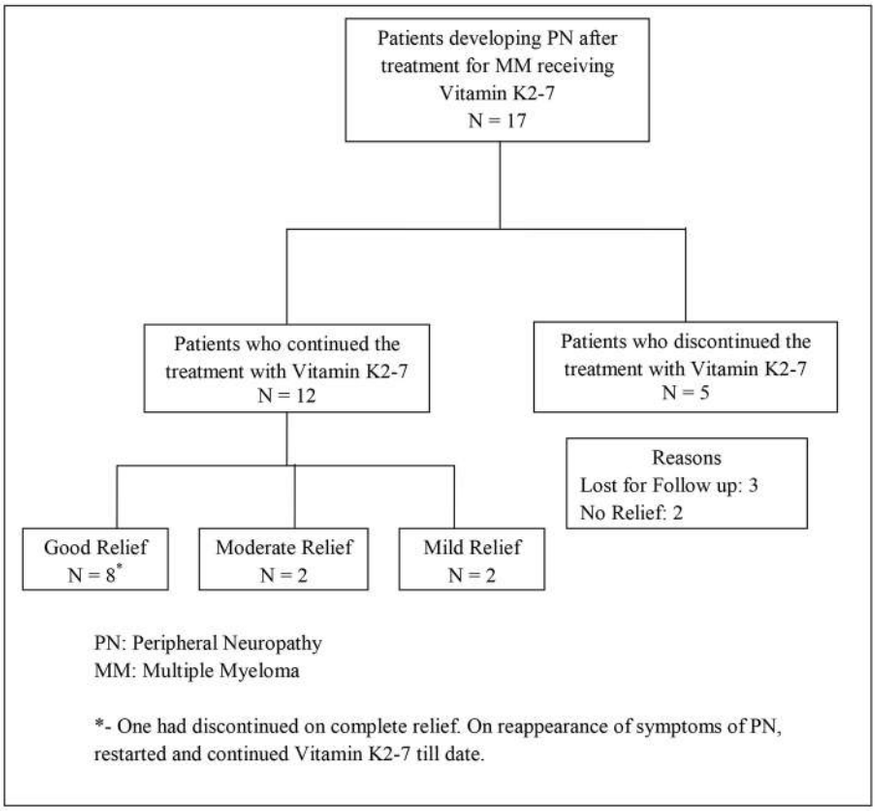
MM: Multiple Myeloma, PN: Peripheral Neuropathy, T: Tingling, N: Numbness, B: Burning
Complete Relief: All symptoms of PN disappeared completely giving immense relief
Moderate Relief: Symptoms of PN decreased partially but not completely
Mild Relief: Reduction in symptoms up to a lesser extent

Discussion

Iatrogenic PN typically is seen in patients with MM who received chemotherapy. It is primarily of a sensory or sensorimotor nature, and the symptoms of tingling, numbness, burning sensation and pain are predominantly bilaterally symmetric. Severity may vary from mild intensity to severe enough so as to require discontinuation of therapy [8]. Thus, any modality that would reduce the severity and allow continuation of effective therapy is the need in a clinical setting.

Patients have earlier described burning pain, numbness or tingling in hand and feet, altered sensitivity to touch and heat, weakness in muscle and a lack of muscular coordination. More common are sensory neuropathy and neuropathic pain. Additionally, sensory PN can lead to areflexia and loss of proprioception. Symptoms or signs of motor

Fig. 1. Study Flow Chart



and/or autonomic nervous system damage can also emerge. Motor symptoms prevalently occur in the case of a severe sensory PN causing muscle cramps, muscle atrophy, or loss of strength in distal muscles. Rarely, orthostatic hypotension, bradycardia, constipation, or impotence can occur as signs of autonomic neuropathy [9,10]. In the present series, latter two were not observed.

In the management of MM, over the past decade, new treatment options, such as the proteasome inhibitor (PI) bortezomib and the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, have dramatically changed the outcome of MM patients, improving response and long-term survival [10]. These new drugs have enhanced and altered the paradigm of MM management, for either newly diagnosed or relapsed/refractory patients. However, these compounds are not free from side effects [11,12].

In practice, one of the major challenges in the treatment of MM is the development of debilitating drug-induced PN affecting compliance leading to discontinuation of therapy or dose/drug modification [13].

PN is significant dose-limiting toxicity of bortezomib. Grade 1 or Grade 2 PN that can influence the therapeutic outcome. Neural damage can be observed at the onset of the disease, due to the effect of monoclonal protein or compressive radiculopathy, but more often it is treatment related. Thalidomide and bortezomib are mainly responsible for PN. Degeneration of dorsal root ganglion is common, prevalently related to angiogenesis inhibition and cytokine modulation in the case of thalidomide and inhibition of the ubiquitin-proteasome system in the case of bortezomib. Lenalidomide does not seem to cause substantial neurotoxicity [14].

It is interesting to know that vitamin K2-7 is useful in reducing the symptoms of PN. Two of the authors (DSM and ABV) had earlier serendipitously observed that vitamin K2-7 relieves idiopathic muscle cramps and symptoms of neuropathy. The patent PCT/IN2008/000465 further claims, besides relief of cramps, the safety of vitamin K2-7 and its novel use in conditions like neuropathy [15]. Taking a lead from this discovery, an open-labeled observational study was conducted which shows that oral dose of vitamin K2-7 100 mcg for 3 months is associated with a reduction of intensity, frequency, and duration of idiopathic muscle cramps [16]. Toxicity studies conducted by Ravishankar *et al*. have shown that Vitamin K2-7 is non-toxic up to a dose of 20000 mg.[17]

Based on this observation, Kulkarni *et al* in 2009 conducted an open-labeled reverse pharmacology study for vitamin K2-7 (MK-7) in 30 patients of PN suffering from a deficiency of vitamin B12 deficiency and /or diabetes mellitus. Administration of vitamin K2-7 100 mcg twice a day for 8 weeks was tolerated and safe with therapeutic activity for symptoms of PN [7]. Recently an open-labeled efficacy and safety study of vitamin K2-7 was conducted in 100 patients presenting with PN and suffering from either vitamin B12 deficiency and/ or type 2 diabetes mellitus by Mehta *et al*. Vitamin K2-7 at a dose of 100 mcg twice a day for eight weeks was given to the patients and were followed up to twelfth week. The decrease in the symptoms of PN as recorded on Visual Analog Scale was found to be statistically significant ($P<0.0001$) [18].

The above case reports indicate that vitamin K2-7

reduces the symptoms of PN like tingling, numbness, burning sensation, pain, causalgia, wooly feeling and cramps caused during treatment of MM. The therapeutic activity of vitamin K2-7 noted in this case series needs to be followed up with a large scale, multi-centric and long-term clinical trial with objective markers like nerve conduction velocity in patients of MM with PN.

Tolerability and Safety

Vitamin K2-7 was well tolerated clinically by all patients. No adverse events were reported during the period of therapy. The organ function tests did not show any adverse effects.

Conclusions

Patients receiving therapy for MM reported a spectrum of symptoms of PN like tingling, numbness and burning sensation. The current preliminary observational data suggest that Vitamin K2-7 is useful in the treatment of PN caused due to the therapy of MM. This initial observational study of therapeutic relief of iatrogenic PN in MM patients needs to be evaluated in a larger sample size along with the use of semiquantitative instruments like Visual Analog Scale and an objective marker like Nerve Conduction Velocity.

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