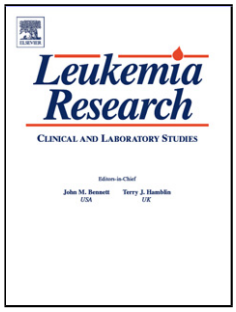

Title: Neurotoxicity of stem cell mobilization chemotherapy with vinorelbine in myeloma patients after bortezomib treatment

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Highlights:

- Vinorelbine chemotherapy with G-CSF is a reliable and effective mobilization regimen in myeloma patients.
- However, a single vinorelbine administration is adding significant neurotoxicity in bortezomib-pretreated myeloma patients.
- Aggravation of bortezomib-induced neuropathy was observed in 17%, and first occurrence of polyneuropathy in additional 7% patients.
- Development of polyneuropathy was not associated with differing survival rates.
- The efficacy of vinorelbine mobilization should be balanced against its neurotoxic potential.

Neurotoxicity of stem cell mobilization chemotherapy with vinorelbine in myeloma patients after bortezomib treatment.

Myeloma Article

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Key words: mobilization, stem cells, myeloma, polyneuropathy, vinorelbine, bortezomib, neurotoxicity.

Running head: Vinorelbine mobilization induces polyneuropathy.

Abbreviations: MM: multiple myeloma; HDCT: high-dose chemotherapy; ASCT: autologous stem cell transplantation; G-CSF: granulocyte-colony stimulating factor; PN: peripheral neuropathy; CIPN: chemotherapy-induced peripheral neuropathy; BIPN: bortezomib-induced peripheral neuropathy; VD: bortezomib dexamethasone; VCD: bortezomib, cyclophosphamide and dexamethasone; PAD: bortezomib, doxorubicin and dexamethasone; VTD: bortezomib, thalidomide and dexamethasone; VRD: bortezomib, lenalidomide and dexamethasone; VG: vinorelbine and G-CSF; VP: vinorelbine and plerixafor; VGP: vinorelbine, G-CSF and plerixafor; OS: overall survival; PFS: progression-free survival

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ABSTRACT

Vinorelbine chemotherapy with G-CSF stimulation is the standard mobilization regimen in Switzerland for multiple myeloma patients. However, with the increasing use of bortezomib during induction treatment, adding the neurotoxic compound vinorelbine for mobilization may aggravate bortezomib-induced polyneuropathy. In this retrospective single-center study, we aimed to explore vinorelbine mediated neuropathy in 106 consecutive bortezomib pretreated myeloma patients. We confirmed that vinorelbine with G-CSF represents a reliable and effective regimen for mobilization of autologous stem cells. However, the single administration of 35mg/m^2 vinorelbine added significant neurotoxicity. We found that 24 patients (24%) reported vinorelbine mediated neurotoxicity: Aggravation of bortezomib-induced neuropathy was observed in 17 patients (17%), and vinorelbine mobilization induced first occurrence of polyneuropathy in additional 7 patients (7%). We observed that development of polyneuropathy was not associated with differing survival rates. Finally, affected patients reported polyneuropathy associated disease burden as “very high” in 13% and “high” in 50%. Our data indicate that a single administration of vinorelbine to mobilize autologous stem cells is associated with significant additional polyneuropathy in bortezomib pretreated myeloma patients. The efficacy of vinorelbine mobilization should be balanced against its neurotoxic potential.

1. INTRODUCTION

Treatment algorithms for multiple myeloma (MM) patients have rapidly evolved in the last decade. Introduction of thalidomide, bortezomib or lenalidomide into induction treatment, the routine use of high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT), and subsequent consolidation and maintenance treatment with bortezomib or lenalidomide have markedly improved prognosis of young myeloma patients [1,2]. In particular, the response to induction treatment has been increasingly improved with impressive rates of complete remission. Also, HDCT with ASCT continues to add independent additional benefit in the era of novel agents, and, finally, maintenance treatment after HDCT was demonstrated to significantly prolong progression-free survival and – at least in some studies – also overall survival [3,4]. Thus, HDCT supported by ASCT remains a cornerstone of the standard treatment algorithms for myeloma patients aged below 65 years [1,5].

For the collection of autologous hematopoietic stem cells, the use of peripheral blood stem cells has become the preferred procedure. However, the optimal strategy to mobilize autologous stem cells from the bone marrow to the peripheral blood remains controversial [6]. CD34+ cells can effectively be mobilized with granulocyte colony-stimulating factor (G-CSF) alone or in combination with chemotherapy, or - in patients with insufficient mobilization potential - together with the stem cell mobilizing compound plerixafor, with combinations of these modalities being superior compared to G-CSF alone. Given the costs of plerixafor, the combination of chemotherapy with G-CSF remains a widely used strategy. Whereas high-dose cyclophosphamide chemotherapy with G-CSF represents the most commonly used chemomobilization regimen, the combination of G-CSF with a single dose of non-myelosuppressive chemotherapy with vinorelbine (35mg/m^2) represents the standard mobilization regimen in Switzerland since a decade [7-10]. Its advantages compared to cyclophosphamide mobilization include a highly predictable collection rate at day 8, its strictly

ambulatory setting, and the lack of febrile complications notoriously associated with cyclophosphamide mobilization [7-10].

With the predominant use of bortezomib during induction treatment and with chemotherapy-induced polyneuropathy (CIPN) as its limiting side effect, the use of vinorelbine might have become increasingly problematic because of its additional neurotoxicity [11-13]. Severe aggravation of pre-existing peripheral neurotoxicity (such as diabetic, alcoholic or inherited neuropathy) and CIPN in patients with concomitant or previous treatment with other neurotoxic chemotherapy compounds such as paclitaxel have been reported following vinorelbine treatment [11,14-16]. These facts led us to evaluate vinorelbine-induced CIPN following mobilization treatment in MM patients.

2. MATERIALS AND METHODS

2.1 Patients and study design:

This single-center retrospective study comprised all consecutive myeloma patients undergoing first-line consolidation with high-dose melphalan chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) who were mobilized with a single dose of vinorelbine between 01/2005 and 01/2013. This study was restricted to patients who received a bortezomib-based induction treatment. Patient characteristics at diagnosis are summarized in **Table 1** including information on the chemotherapy regimens used. This study was approved by the local ethics committee of Berne, Switzerland (decision #143/2014).

Data sources were medical records of the patients. In addition, a detailed questionnaire assessing existence and severity of neuropathy was sent to patients who underwent the mobilization procedure between 01/2011 and 01/2013. The purpose of this questionnaire was to gather information on the subjective disease burden of chemotherapy induced polyneuropathy, but also to verify the information retrieved from the medical records. We decided against sending the questionnaire to patients mobilized before January 2011 as such an analysis might have generated unreliable information. Accordingly, 41 questionnaires were sent out, with a 100% response rate.

2.2 Stem cell chemomobilization and transplantation procedure:

Vinorelbine was given to all patients as a 10 minute infusion at 35 mg/m^2 on day 1. Filgrastim (G-CSF) was administered subcutaneously at a dose of 1 Mio U/kg/day divided into two daily doses. It was started on day 4 and continued until the day of stem cell collection. Apheresis was consistently initiated at the first day when the peripheral blood CD34+ cell count exceeded 10'000 cells/ml. A minimum of 2x10^6 collected CD34+cells/kg b.w. was required. Cell processing procedures followed local standards. All patients

underwent high-dose chemotherapy with melphalan administered intravenously at a dose of 200mg/m^2 with peripheral stem cell transplantation at the following day.

2.3 Definitions:

The primary endpoint of the study was CIPN following vinorelbine mobilization treatment. We assessed CIPN occurring during induction, mobilization, high-dose and maintenance treatment. We analyzed incidence, severity, localization, and specific treatment. CIPN during mobilization chemotherapy was defined as vinorelbine-induced, when patients presented novel or increased symptoms within seven days after its administration. CIPN during bortezomib-based induction treatment was defined, when it occurred between the first bortezomib administration and up to 30 days after the last dose. Quality and severity of CIPN were assessed according to the modified version of the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE; version 4.03). The following categories were assessed: general sensory neuropathy (paresthesia, dysesthesia, hypesthesia, hyperesthesia, hyporeflexia, hypalgesia, and decreased temperature sensation); neuropathic pain; general motoric neuropathy (muscle weakness); fasciculation (including tremor and spasm); and ataxia. We also determined the need for specific analgetic CIPN medication as well as modification or interruption of myeloma specific treatment to control CIPN symptoms.

2.4 Statistical analysis:

Descriptive statistics were used to calculate variables. For continuous variables, we summarized number of observations, median and range. For categorical data, number and percentage of patients in each category were calculated. We compared nominal variables with Fisher exact tests. For continuous variables, we used non-parametric Mann-Whitney-U tests. Response rates were defined according to the IMWG criteria. OS was defined as the time from transplantation until the date of death from any cause or of the last follow-up for patients alive. PFS was defined as the time from transplantation to first progression, relapse or death whichever occurred first and patients without progression or death were censored at

their last follow-up. Time-to-event estimates (PFS, OS) were designed according to the Kaplan-Meier method using the log-rank (Mantel-Cox) test. Data cut-off date was March 1, 2013. All p-values were two-sided. A *P*-value less than .05 was considered statistically significant. All analyses were performed using the GraphPadPrism software (Version 6.0b, GraphPad Software, Inc, San Diego, CA).

3. RESULTS

3.1 Patient demographics, baseline characteristics and treatment regimens:

In this cohort, we investigated 106 consecutive myeloma patients who received bortezomib-based first-line induction chemotherapy and who were subsequently mobilized using a vinorelbine-based regimen. Patient characteristics at diagnosis and details on the chemotherapy regimens are summarized in **Table 1**. The median age at diagnosis of the patients in our cohort was 58 years (range 39-69 years). Patients mostly had IgG subtype (68%), kappa light chain involved (58%), and ISS stage I (41%). Cytogenetic analyses were available in 55 patients (52%), with high-risk abnormalities in 36 of these 55 patients (65%).

62 of the 106 patients (59%) received an induction regimen with bortezomib / dexamethasone (VD), 27 patients (25%) had a combination of bortezomib / cyclophosphamide / dexamethasone (VCD), 12 patients (11%) had a regimen with bortezomib / doxorubicin / dexamethasone (PAD), 2 patients (2%) had bortezomib / thalidomide / dexamethasone (VTD), and 3 patients (3%) were treated with bortezomib / lenalidomide / dexamethasone (VRD), respectively. Bortezomib was given at a dose of 1.3 mg/m^2 at days 1, 4, 8 and 11 every three weeks. Until 12/2010, bortezomib was administered intravenously, whereas it was given subcutaneously since 01/2011. For patients developing neuropathy, bortezomib treatment was first modified in terms of dose (1.0 mg/m^2, then 0.8 mg/m^2), and second altered to a once weekly schedule. 45 patients (42%) received maintenance treatment most frequently with lenalidomide (93%), and in 7% with bortezomib.

3.2 Mobilization, apheresis and transplantation:

Mobilization, apheresis and transplantation details are given in **Table 2**. 75 patients (71%) received a mobilization treatment with vinorelbine and G-CSF (VG), 21 patients (20%) had vinorelbine and plerixafor (VP) without G-CSF, and 10 patients (9%) received a combination of vinorelbine, G-CSF and plerixafor (VGP). In 92 patients (87%), a single day apheresis procedure was sufficient to collect the target number of at least 2 x 10^6 CD34+cells/kg body

weight (b.w.), whereas 14 patients (13%) needed two collection days. Apheresis was started after a median of 8 days (range 7 to 16 days) after mobilization with vinorelbine, and it was accomplished within a median of 228 minutes (range 70 to 453 minutes). The median final CD34+ apheresis yield was 13.55 x 10^6 cells/kg b.w. (range 3.09 to 37.33). More than 10 x 10^6 CD34+ cells/kg b.w. were collected in 75% of patients.

All patients ultimately proceeded to HDCT with melphalan and ASCT, and patients received a median of 4.34 x 10^6 CD34+ cells/kg b.w. (range 2.04 to 8.45). All patients had successful engraftment. The median time to recovery was 12 days (range 10 to 15 days) for neutrophils, 13 days (range 8 to 23 days) for platelets > 20x10^9/l, and 21 days (range 14 to 87 days) for platelets > 100x10^9/l.

3.3 Chemotherapy induced polyneuropathy (CIPN):

The incidence of CIPN during induction and mobilization treatment is summarized in **Table 3**. In five patients (5%), polyneuropathy was pre-existing - due to diabetes mellitus, was myeloma-associated or had an unknown cause. More than half of all patients developed CIPN during bortezomib-based induction treatment: Non-significant differences were observed in the total incidence of CIPN as documented by the treating physicians in their medical charts (58%) compared to the data retrieved from individual questionnaires (62%; *P* = .4561).

CIPN symptoms were first reported after a median of seven weeks of bortezomib treatment according to the physician's charts as compared to patients reporting in their questionnaire the onset of symptoms already after four weeks (*P* = .0232). As depicted in **Table 4**, CIPN affected patients predominantly reported sensory symptoms (95%), with grade I/II in 78% and grade III/IV in 22%. Mild to severe neuropathic pain was documented in 24%. Motoric symptoms were underreported in the medical records compared to the questionnaires, with muscle weakness (10% versus 37%; *P* = .0050), and with spasms, tremor or fasciculations in 10% versus 30% (*P* = .0263). Whereas physicians rarely documented ataxia (5%), 22% of the patients reported signs of ataxia (*P* = .0205). In

conclusion, as compared to individual questionnaires, medical records congruently documented the total incidence of CIPN and the occurrence of sensory deficits as the predominant form of CIPN, but not additional manifestations of CIPN in affected patients.

Any kind of treatment for CIPN was noted in 30% based on medical charts, but was reported in 44% in the patient questionnaires (*P* = .0387). Medication predominantly comprised pregabalin, gabapentin and opioids. Finally, 19% of all patients needed bortezomib dose reduction, prolongation of treatment interval or even interruption of therapy. In 13% of all patients, CIPN resulted in the discontinuation of bortezomib treatment.

The development of CIPN following vinorelbine mobilization chemotherapy is presented in **Table 3.** Based on medical charts, 24 of 106 patients (23%) reported CIPN following vinorelbine mobilization chemotherapy (17 patients reported worsening of pre-existing CIPN and 7 patients developed novel CIPN); in accordance, 11 (of 41) patients (27%) also reported this in their questionnaire (*P* = .6668). Details of CIPN during mobilization are given in **Table 4**. Sensory deficits were reported in 96% (n=23) of the patients, with grade I/II in 61%, and in 39% with grade III/IV. Neuropathic pain was observed in 33%, with grade III/IV in 75% of affected patients. Again, patients reported motoric deficits more frequently in the questionnaires both for motoric PN (36%) and spasms/tremor/fasciculations (45%) compared to the medical records with 0% for motoric CIPN and 13% for spasms/tremor/fasciculations (*P* = .0063, and *P* = .0767, respectively). Ataxia was not reported in the medical charts, but 18% of patients in the questionnaire experienced ataxia during mobilization therapy (*P* = .0924). 50% of all patients needed analgesic medication medication such as pregabalin, gabapentin, paracetamol or metamizol against CIPN following vinorelbine mobilization chemotherapy.

Reporting of new or worsening of CIPN due to HDCT was rare, with 5% according to the medical charts (**Table 3)**. Similarly, the rate of new or worsening of pre-existing CIPN caused by maintenance treatment was low, with an incidence of 13% in the medical charts versus 10% in the questionnaire (*P* = .7302). Both patients in our cohort treated with

thalidomide maintenance also developed CIPN, compared to 10% of all patients treated with lenalidomide maintenance **(Table 3)**.

Follow-up information on the course of CIPN was available for all patients who developed CIPN during the treatment procedure and who participated in the questionnaire part of the study. 5% of all patients with CIPN became asymptomatic with the end of HDCT, and in 22% symptoms improved gradually over time with a median time to improvement of 3 months (range 1 to 8 months). However, 31% of the patients in the questionnaire reported a partial improvement of CIPN, and 31% of the patients with CIPN reported unchanged symptoms. Patients described a “very high burden” due to CIPN in 13%, and a “high burden” in 50%. For 31% of the patients, CIPN was “tolerable and modest”, whereas only 6% considered it “harmless” (data not shown).

3.4 Response to treatment and outcome:

When comparing patients with and without CIPN before ASCT, we observed non-significant differences in the response rates before ASCT between these groups: The CR, VGPR, and PR rates were 10% versus 19%, 13% versus 25% and 73% versus 56%, respectively. Also, we found non-significant differences in the response rates between the two groups 100 days after ASCT, with the CR rates tending to be lower in patients with CIPN (with 43% versus 62%; *P* =.0722).

The group of myeloma patients with CIPN had a longer follow-up (23 versus 16 months; *P* = .0294). **Figure 1A** depicts the progression-free survival (PFS) of the two groups, and **Figure 1B** indicates the overall survival (OS). We observed no significant differences in survival rates. The median PFS of patients with CIPN was 16 months (range 1 to 59 moths) compared to 12 months (range 1 to 79 months) of patients without CIPN (*P* = .6906); and the median OS of patients with CIPN was 23 months (range 1 to 64) compared to 17 months (range 1 to 79) of patients without CIPN (*P* =.8761).

4. DISCUSSION

Current practice in Switzerland for stem and progenitor cell mobilization in myeloma patients consists in the combination of chemotherapy with vinorelbine and daily G-CSF administration followed by stem cell apheresis consistently scheduled on day 8. The advantages of this strategy compared to cyclophosphamide mobilization include a highly predictable collection rate at day 8, its strictly ambulatory setting, and the lack of febrile complications notoriously associated with cyclophosphamide mobilization. This – to some degree local – strategy has been challenged in the last years with the predominant use of bortezomib during induction treatment and with bortezomib induced polyneuropathy (CIPN) as its major side effect. This study aimed to investigate concerns on the use of vinorelbine in myeloma patients presenting with bortezomib mediated CIPN. In fact, we found in our cohort of 106 consecutive bortezomib pretreated myeloma patients that a single administration of 35 mg/m^2 vinorelbine added significant neurotoxicity. We observed in 24% of all patients vinorelbine caused neurotoxicity. Aggravation of bortezomib-induced neuropathy was observed in 17%, and vinorelbine mobilization induced first occurrence of polyneuropathy in 7%.

The use of bortezomib-based regimens during first-line induction treatment has become standard of care for myeloma patients, with CIPN being its major and often limiting side effect [17-23]. Consequently, grade 3-4 neuropathy was reported in 4% to 27% in pevious series, and we observed a frequency of 23% in our cohort. In addition, we found in bortezomib-treated myeloma patients the development of novel (or worsening of pre-existing) neuropathy in 58% of all patients. The majority of the patients had sensory deficits which is consistent with previous reports on bortezomib inducing a dose-related peripheral mainly sensory polyneuropathy with accompanying neuropathic pain [17-23]. A surprising finding of our study was that patients in our cohort tended to report motoric impairment more frequently (37%) if asked in detail whereas such deficits were previously reported to occur in only up to 10% of the patients [17]. Similar findings were observed for the development of ataxia. Most liekly, physicians are impressed by the more frequent sensory deficits often associated with

neuropathic pains leading to underreporting of signs of motoric neuropathy such as muscle weakness, spasms, fasciculations or tremor [17].

Our data suggest that a single administration of 35 mg/m^2 of vinorelbine mobilization treatment can induce relevant additional or novel neurotoxicity in a significant proportion of bortezomib-pretreated myeloma patients. Vinorelbine mediated neurotoxicity is considered to be less frequent compared to other vinca-alkaloids. Vinca-alkaloids mediate neurotoxicity based on their affinity for β-tubulin, the subunit of microtubules, thereby suppressing not only the dynamics of the mitotic spindle, but also leading to destabilization of the axonal microtubules and consequently to axonal damage [11,13,24,25]. Vinorelbine is considered to cause less neurotoxicity than other vinca-alkaloids due to a more selective binding to mitotic than to axonal microtubules, and therefore higher concentrations of the drug are needed to cause neurotoxicity [13,26-29]. In fact, previous reports indicated a dose-dependent neurotoxicity of vinorelbine treatment with predominantly distal peripheral sensory polyneuropathy [11,13,30]. The most common symptoms were hypoesthesia, hyporeflexia, paresthesia and pain, but also motoric or autonomic axons were involved, which is similar to the neurotoxic profile of bortezomib [11,12,21,27,30,31].

Vinorelbine toxicity typically occurs in the setting of cumulative administrations [13,30]. The dose of vinorelbine in our study was 35 mg/m2 administered once compared with 25 to 30 mg/m2 administered weekly when used in other cancer treatment regimens [11,12]. Repetitive administration of vinorelbine was reported to induce symptoms of mild to moderate neuropathy in 30 to 85% of patients after three to four weeks. After prolonged administration, almost all patients ultimately develop neurotoxic side effects, but neurotoxicity grade III/IV is usually observed in less than 5% of the patients [13,26,27,32]. Both single and cumulative dose turned out to be significant risk factors for the development of vinorelbine mediated neurotoxicity [13].

Rapid aggravation of pre-existing peripheral neurotoxicity – such as diabetic, alcoholic or inherited neuropathy - and rapid induction of novel CIPN have been reported following vinorelbine treatment in patients with prior or concomitant exposure to other

neurotoxic agents, mainly taxanes, anthracyclins, cisplatin or ifosfamide [11,13-16,33-37]. In particular, vinorelbine-paclitaxel combinations were found to enhance pre-existing polyneuropathy, with an increased risk for further neurotoxicity even in moderate doses of vinorelbine and even after a one-year interval until next vinorelbine administration [14-16,34,38]. These findings underline the vulnerability for further aggravation of neurotoxicity following vinorelbine treatment when used after other neurotoxic compounds such as bortezomib, though the underlying mechanisms may not yet be fully understood [34].

Recently, the late onset of previously not overt bortezomib induced polyneuropathy was reported, emerging mainly during or shortly after peripheral blood stem cell (PBSC) collection. A coasting phenomenon of bortezomib was suggested rather than an effect of compounds used between bortezomib-based induction treatment and PBSC collection [39]. However, our data suggest that vinorelbine can independently add to bortezomib-caused CIPN [20,21,41].

We observed a slow recovery rate from bortezomib-vinorelbine triggered polyneuropathy. In fact, half of all affected patients continued to suffer from symptoms of disabling CIPN after completion of HDCT treatment. Previous reports suggested that bortezomib- or vinorelbine-induced neuropathy were predominantly reversible after drug discontinuation within two to four months [17,18,21,30,42,43]. In contrast, improvement of CIPN in our cohort remained incomplete in a significant proportion of patients. In the absence of effective treatment modalities for CIPN, prevention of severe CIPN remains a major goal of induction treatment in myeloma patients [44].

This study was not powered to evaluate the effect of the development of CIPN on response and survival rates. In fact, we observed no significant differences in response and survival rates between myeloma patients with and without CIPN. However, developing CIPN can affect dosing, duration and the chemotherapy composition of myeloma treatment thereby affecting response to treatment [45]. Consequently, longer follow-up of a larger cohort may be required to ultimately provide answers to these issues.

5. CONCLUSIONS:

Our data suggest that a single administration of vinorelbine mobilization chemotherapy can induce relevant novel CIPN or increase pre-existing CIPN in myeloma patients after bortezomib-based induction chemotherapy. The majority (63%) of affected myeloma patients considered the burden of CIPN as “high” or “very high”, and the majority failed to completely recover from CIPN, with 31% reporting unchanged persisting CIPN after completion of HDCT treatment. Whereas the advantages of non-myelosuppressive mobilization chemotherapy - as opposed to high-dose cyclophosphamide – still remain significant, these observations indicate that vinorelbine mobilization chemotherapy is associated with significant additional neurotoxicity in bortezomib pretreated myeloma patients and that alternative non-neurotoxic chemotherapeutic agents need to be evaluated for stem cell mobilization. In our view, gemcitabine represents a promising candidate which has been mainly studied so far for mobilization in Hodgkin lymphoma patients [46-48]. Consequently, we initiated a randomized prospective trial comparing vinorelbine and gemcitabine mobilization chemotherapy in myeloma patients and this trial may ultimately identify a novel role for gemcitabine as a non-neurotoxic and effective stem cell mobilization regimen in myeloma patients.

One might argue that mobilization chemotherapy can be omitted at all in patients with significant neuropathy. In fact, bortezomib based combinations as induction in young patients do not compromise peripheral blood stem cell collection, and most patients collect CD34+ cells enough for one or two transplants using G-CSF alone. However, the combination of chemotherapy and G-CSF allows more potent mobilization of peripheral autologous stem cells resulting in shorter apheresis procedures and lower costs. This is highlighted by the fact that 87% of all stem cell collections after vinorelbine/G-CSF stimulation in our cohort could be finished in a single day apheresis procedure, whereas this rate is usually decisively lower using G-CSF alone mobilization strategies. Thus, a strong rationale is persisting for a combined chemotherapy/G-CSF mobilization strategy which should acknowledge preexisting polyneuropathy.

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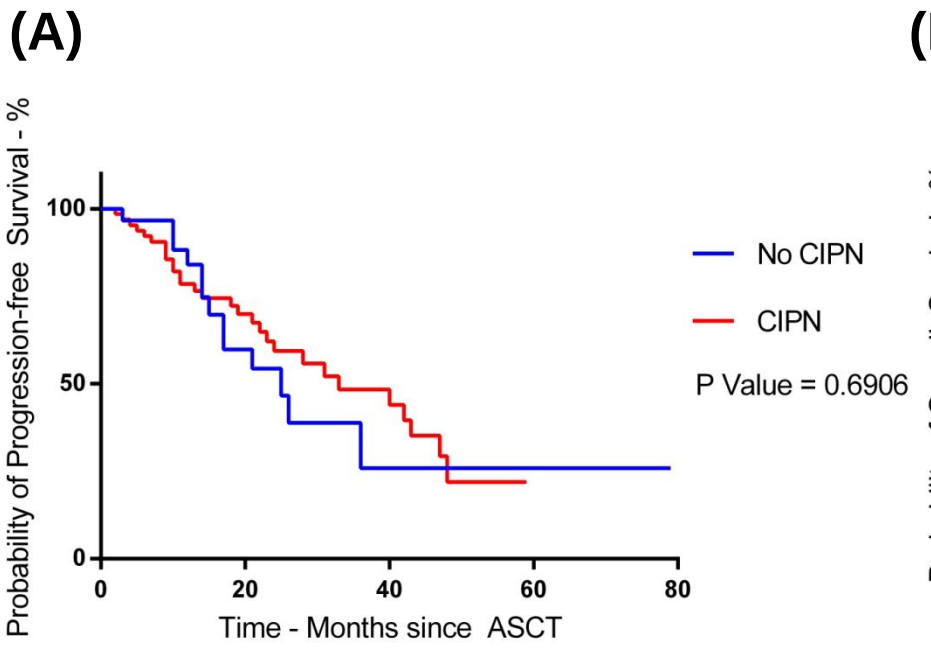
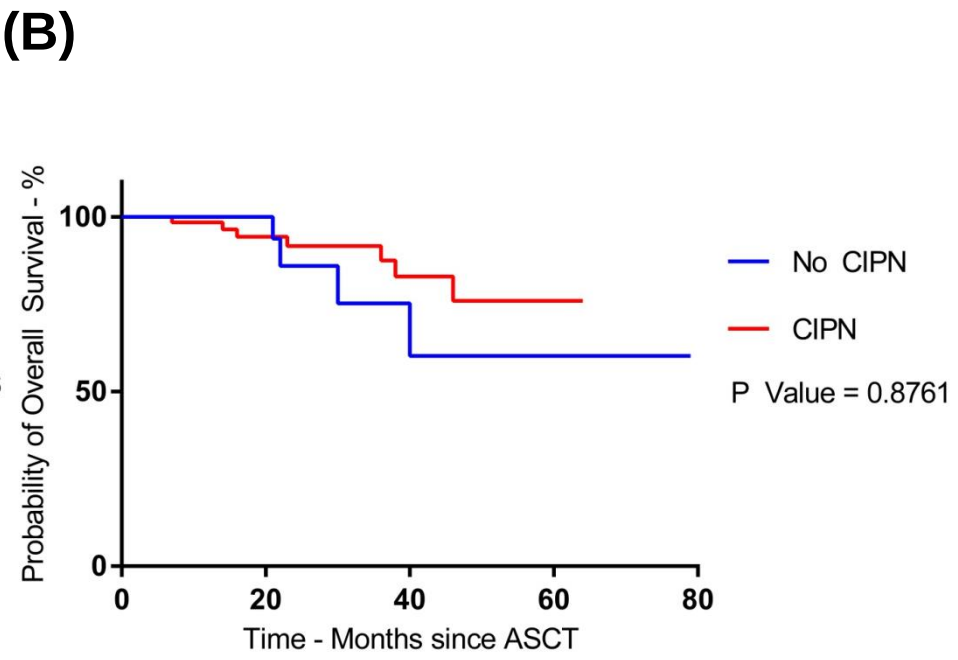
8. Figure 1


(A)
Probability of Progression-free Survival - %
100
50
0
0
20
40
60
80
Time - Months since ASCT
No CIPN
CIPN
P Value = 0.6906


(B)
Probability of Overall Survival - %
100
50
0
0
20
40
60
80
Time - Months since ASCT
No CIPN
CIPN
P Value = 0.8761

9. FIGURE LEGEND

Figure 1:

A) Kaplan-Meier curves are depicted for progression free survival (PFS) and **B)** overall survival (OS) comparing myeloma patients with chemotherapy induced polyneuropathy (CIPN) versus patients without CIPN during first-line treatment including bortezomib-based induction chemotherapy, vinorelbine mobilization treatment and high-dose chemotherapy with melphalan supported by autologous stem cell transplantation.

10.1 Table 1: Patient characteristics and therapy regimens.	
	n = 106
Age, years, median (range)	58 (39 – 69)
Sex, male / female, n	67 / 39
Paraprotein IgG, n (%)	72 (68)
IgA, n (%)	18 (17)
IgM, n (%)	2 (2)
light-chain only, n (%)	14 (13)
Light chain kappa involved, n (%)	62 (58)
lambda involved, n (%)	44 (42)
Durie & Salmon stage I, n (%)	35 (33)
II, n (%)	27 (25)
III, n (%)	44 (42)
A, n (%)	81 (76)
B, n (%)	25 (24)
ISS stage I, n (%)	43 (41)
II, n (%)	30 (28)
III, n (%)	33 (31)
Cytogenetic/FISH analysis available, n (%)	55 (52)
no abnormalities, n (%)	3 (3)
standard risk, n (%)	16 (15)
high risk, n (%) [a)]	36 (34)
Induction regimens, n (%) [c)]	
bortezomib, dexamethasone (VD)	62 (59)
bortezomib, cyclophosphamide, dexamethasone (VCD)	27 (25)
bortezomib, doxorubicin, dexamethasone (PAD)	12 (11)
bortezomib, thalidomide, dexamethasone (VTD)	2 (2)
bortezomib, lenalidomide, dexamethasone (VRD)	3 (3)
Induction regimen, cycles, median, n (range)	4 (1 – 10)
Maintenance therapy, n (%)	45 (42)
lenalidomide	42 (94)
thalidomide	2 (4)
rituximab [b)]	1 (2)

[a)] High-risk cytogenetics comprised hypodiploidy, deletion of chromosome 13 or 17p, presence of t(4;14) or t(14;16), or amplification of chromosome 1. All other abnormalities were considered standard risk; FISH: fluorescence in situ hybridization; ISS: international staging system. [b)] Given in one patient with CD20 positive myeloma who did not tolerate lenalidomide. [c)] 101 of 106 patients had 3 or 4 cycles of bortezomib-based induction treatment.

10.2 Table 2: Mobilization, apheresis and autologous stem cell transplantation.	
	n = 106
Mobilization regimen:	
vinorelbine, G-CSF [a] (VG), n (%)	75 (71)
vinorelbine, plerixafor (VP), n (%)	21 (20)
vinorelbine, G-CSF, plerixafor (VGP), n (%)	10 (9)
Apheresis days:	
only 1, n (%)	92 (87)
≥1 needed, n (%)	14 (13)
Days until apheresis, median (range)	8 (7 – 16)
Duration of apheresis per day, minutes, median (range)	228 (70 – 453)
Peripheral WBC [b] count, x 10^9/l, median (range)	24.60 (2.50 – 54.34)
Peripheral CD34+ cells, x 10^6/l, median, (range)	104.35 (5.00 – 378.00)
Peripheral CD34+ cells at apheresis, median, % (range)	0.43 (0.02 – 2.82)
Final CD34+ apheresis yield x 10^6/kg, median, (range)	13.55 (3.09 – 37.33)
≥ 2 x 10^6 / kg	2 (2)
≥ 5 x 10^6 / kg	24 (23)
≥ 10 x 10^6 / kg	80 (75)
Transplantation:	
Transplanted CD34+ cells x 10^6/kg, median, (range)	4.34 (2.04 – 8.45)
Days until neutrophil recovery >0.5x10^9/l, median, n (range)	12 (10 – 15)
Days until platelet recovery >20x10^9/l, median, n (range)	13 (8 – 23)
Days until platelet recovery >100x10^9/l, median, n (range)	21 (14 – 87)

[a] Granulocyte colony stimulating factor; [b] white blood cell count.

10.3 Table 3: Chemotherapy induced polyneuropathy (CIPN).	
	n = 106
Preexisting neuropathy [a)], n (%):	5 (5)
CIPN during induction therapy, n (%):	
no CIPN	44 (42)
first occurrence or worsening of neuropathy	62 (58)
worsening of preexisting neuropathy	2 (3)
first occurrence of neuropathy	60 (97)
CIPN first occurrence, weeks since start treatment, median (range)	7 (1 – 21)
CIPN following mobilization therapy, n (%):	
no CIPN	37 (35)
preexisting CIPN unchanged or improved	45 (42)
first occurrence or worsening of neuropathy	24 (23)
worsening of preexisting neuropathy	17 (71)
first occurrence of neuropathy	7 (29)
CIPN following HDCT, n (%):	
no CIPN	34 (32)
preexisting CIPN unchanged or improved	67 (63)
first occurrence or worsening of neuropathy	5 (5)
worsening of preexisting neuropathy	2 (40)
first occurrence of neuropathy	3 (60)
CIPN during maintenance therapy, n (%):	n = 45 (100)
no CIPN	16 (36)
preexisting CIPN unchanged or improved	23 (51)
first occurrence or worsening or reoccurrence of neuropathy	6 (13)
worsening or reoccurrence of preexisting neuropathy	5 (83)
first occurrence of neuropathy	1 (17)
maintenance, n with CIPN per n patients with this regimen, (%)	
lenalidomide	4 / 42 (10)
thalidomide	2 / 2 (100)
rituximab	0 / 1 (0)

[a)] due to: diabetes mellitus (n=2), myeloma associated (n=2), or unknown (n=1).

10.4 Table 4. Characteristics of first occurrence or aggravated chemotherapy induced polyneuropathy (CIPN).

First occurrence of CIPN or worsening of CIPN during	induction therapy n=62	mobilization n=24
Quality and severity, n (% of patients with CIPN) [a]		
peripheral sensory neuropathy [b]	59 (95)	23 (96)
I / II	46 (78)	14 (61)
III / IV	13 (22)	9 (39)
neuropathic pain	15 (24)	8 (33)
I / II	8 (53)	2 (25)
III / IV	7 (47)	6 (75)
peripheral motoric neuropathy [c]	6 (10)	0 (0)
I / II	5 (83)	0 (0)
III / IV	1 (17)	0 (0)
spasms, tremor or fasciculations	6 (10)	3 (13)
I / II	4 (67)	2 (67)
III	2 (33)	1 (33)
ataxia	3 (5)	0 (0)
I / II	1 (33)	0 (0)
III	2 (67)	0 (0)
Localization, n (% of patients with CIPN)		
lower extremity	24 (39)	10 (42)
upper extremity	10 (16)	1 (4)
lower and upper extremities	27 (44)	13 (54)
other (generalized)	1 (2)	0 (0)
Management, n (% of patients with CIPN) [a]		
no pharmacologic treatment	37 (60)	12 (50)
Pharmacologic treatment [a]	13 (30)	12 (50)
NSAID	1 (8)	2 (17)
paracetamol, metamizol	2 (15)	3 (25)
pregabalin, gabapentin	10 (77)	9 (75)
opioids	3 (23)	2 (17)
magnesium	0 (0)	1 (8)
tricyclic antidepressants	1 (8)	2 (17)
Dose reduction / temporary interruption of therapy	12 (19)	----
Discontinuation of therapy	8 (13)	----

[a] Percentages may sum to more than 100% since some issues may apply more than once in some patients. [b] Peripheral sensory neuropathy included paresthesia, dysesthesia, hypesthesia, hyperesthesia, hyporeflexia, hypalgesia, and decreased temperature sensation. [c] Predominantly included muscle weakness.

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7.1 Contributions:

Performed research and wrote the paper (SK); contributed vital material (UN and BMT); analyzed data (BUM, KS and KL); designed research, analyzed data and wrote the paper (TP).

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