PERIPHERAL NEUROPATHY: ASSOCIATION WITH AGE AND SURVIVAL IN MULTIPLE MYELOMA PATIENTS

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ABSTRACT

***Objective**: Multiple myeloma (MM) accounts for approximately 1% of all cancers and 10% of hematologic malignancies. Peripheral neuropathy (PN) is a common side effect of cancer therapy that can have an impact on quality of life and survivorship. PN may happen in MM due to adverse effect of chemotherapeutics, amyloidosis or as a part of paraneoplastic syndrome. The aim of this study is to evaluate the prevalence of peripheral neuropathy in multiple myeloma patients and its association with age and disease outcome.*

***Materials and methods**: We conducted a retrospective review of 92 multiple myeloma patients who presented to hematology clinic between 2009 and 2014. Their age, gender, performance status, chemotherapeutic regimens, stage of disease, diabetes status and electromyography results were noted. An association between clinical parameters and neuropathy was analyzed. Kaplan Meier analysis was used in statistical comparisons between mortality and other parameters.*

***Results**: The mean age of patients was 64±11.6. Patients with neuropathy were enrolled as group 1 (27.2%) and patients without neuropathy were enrolled as group 2 (72.8%). No significant association was found between age and peripheral neuropathy (p=1.00). The estimated median survival time was 27 months in patients with PN, whereas 56 months in patients without PN (p=0.273). In group 1 three year overall survival rate was 41% whereas in group 2 it was 57%.*

***Conclusion**: It is important to understand pathophysiology of PN and recognize who is at risk since; it is a common side effect of MM treatment. This study is among the few analyses evaluating prevalence of peripheral neuropathy confirmed with electromyography in MM patients. There was no significant association between increased age, survival and neuropathy. Evaluating other associations and understanding potential risks with further research may guide us in developing better preventive and treatment modalities for PN in older MM patients.*

***Key words**: Multiple Myeloma, Peripheral Neuropathy, Electromyography, Elderly.*
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Introduction

Multiple myeloma (MM) accounts for approximately 1% of all cancers and 10% of hematologic malignancies in the United States[(1)]. The median age at diagnosis is 66 years; 10% and 2% of patients are younger than 50 and 40 years, respectively[(2)].

Peripheral neuropathy (PN) is a common side effect of cancer therapy that might affect quality of life and survivorship.

It may affect outcomes of cancer treatment by causing dose modifications and/or treatment discontinuation[(3)]. PN usually consists of sensory rather than motor symptoms and typically has a symmetric, distal, "stocking and glove" distribution. It might be easily overlooked and underreported. It is important to recognize since it might be confused with metastatic disease, paraneoplastic syndromes or comorbid neurologic disorders that do not require dose reduction or discontinuation.

Peripheral neuropathy may happen in MM due to adverse effect of chemotherapeutic agents, amyloidosis or as a part of paraneoplastic syndrome. PN is a common side effect of treatment for patients with MM[4,5]. Thalidomide and bortezomib are effective in MM. But studies have shown that almost 75% of patients treated with thalidomide and half of the patients treated with bortezomib experience PN which cause dose reduction or early termination of chemotherapy[5-10].

Both the incidence and severity of neurotoxicity appear to be higher in patients with preexisting baseline neuropathy and in heavily pretreated patients[11-13]. The available data suggest a neurotoxic dose threshold rather than a classic cumulative dose effect[12-14]. Genetic factors may also contribute[15].

The aim of this study is to evaluate the prevalence of peripheral neuropathy in multiple myeloma patients and its association with age and disease outcome.

Materials and methods

We conducted a retrospective review of 92 MM patients who presented to hematology outpatient clinic at Ataturk Research and Training Hospital, Ankara, Turkey between 2009 and 2014. Patients with neuropathy were enrolled as group 1 (n=25, 27.2%) and patients without neuropathy were enrolled as group 2 (n=67, 72.8%). Their age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), chemotherapeutic regimes (thalidomide or bortezomib or vincristine) and electromyography (EMG) results were noted. Survival estimate of the patients were calculated starting from the diagnosis date until death due to disease or any other cause. An association between age, gender, body mass index (BMI), ECOG performance status, diabetes status, treatment discontinuation rate and neuropathy was analyzed using the chi square test. For the statistics of the study SPSS.20 (IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY: IBM Corp, 2011) software was used. Kaplan Meier analysis was used in statistical comparisons between mortality and other parameters. The association between the variables were considered significant when $p < 0.05$.

Results

The mean age of patients was 64±11.6 and out of 92 patients 57.6% was male. Patients with neuropathy were enrolled as group 1 (n=25, 27.2%) and patients without neuropathy were enrolled as group 2 (n=67, 72.8%). No significant association was found between age and peripheral neuropathy (p=1.00). While the rate of neuropathy was 26.1% in patients 65 and older, it was 28.3% in patients younger than 65. No significant association was found between patient's clinical characteristics and neuropathy (Table 1).

Characteristic	Peripheral neuropathy				
	Yes		No		
	n	(%)	n	(%)	*P*-value
Total	25	27.2	67	72.8	
Age					
65 years ≥	12	48	34	50.7	1.000
65 years <	13	52	33	49.3	
Gender					
Female	10	40	29	43.3	0.817
Male	15	60	38	56.7	
BMI					
25 ≥	9	36	29	43.3	0.636
25<	16	64	38	56.7	
CT					
Bortezomib	11	44	34	50.7	
Thalidomide	11	44	19	28.4	0.315
Vincristine	3	12	14	20.9	
Stage					
Stage 1	10	40	24	35.8	
Stage 2	4	16	14	20.9	0.852
Stage 3	11	44	29	43.3	
DM					
No	22	88	53	79.1	0.385
Yes	3	12	14	20.9	
Treatment discontinuation					
No	20	80	59	88.1	0.330
Yes	5	20	8	11.9	
ECOG PS					
Good	13	52	42	62.7	0.474
Poor	12	48	25	37.3	

Table 1: Baseline clinical characteristics by peripheral neuropathy in multiple myeloma patients.
BMI: Body Mass Index, CT: Chemotherapy , DM:Diabetes Mellitus, ECOG PS: Performance Status

Out of 92 patients, 45 of them (48.9%) were treated with bortezomib, 30 of them (32.6%) were treated with thalidomide and 17 of them (18.4%) were treated with vincristine as first line treatment. Dexamethasone was part of the protocol for each chemotherapeutic regimen. Only 3% of them received bortezomib as second line treatment after thalidomide. While the neuropathy rate was 36.7% in patients who were treated with thalidomide, it was 24.4% in patients receiving bortezomib and 17.6% in patients receiving vincristine. The association between neuropathy and chemotherapeutic agents was statistically insignificant. (p=0.315)

The association of neuropathy with stage of disease, diabetes status and treatment discontinuation rate are shown statistically insignificant (Table 1). A total of 37 patients (40.2%) had poor performance status (ECOG score was 2 or above). The poor performance status was similar between group I and group II (p=0.474).

In survival analysis the estimated median survival time was 27 months in patients with PN, whereas 56 months in patients without PN (p=0.273) (Figure 1). In group 1 three year overall survival rate was 41% whereas in group 2 overall survival rates was 57%.

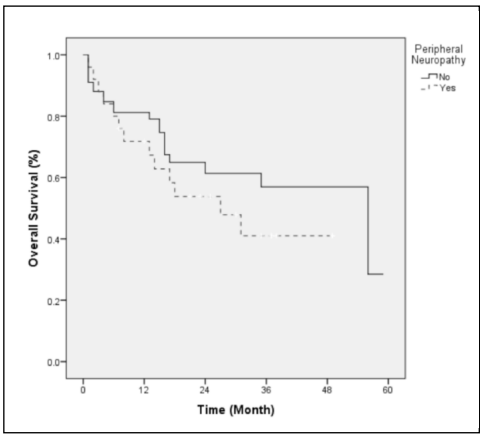

Figure 1: Analysis of overall survival according to the peripheral neuropathy.

Discussion

It is important to understand the pathophysiology of PN and recognize who is at risk since; it is a common side effect of treatment for patients with MM[4,5]. It may affect outcomes by causing dose modifications and/or treatment discontinuation. PN also might affect the quality of life and survivorship. The majority of MM patients are aged > 65 years. The introduction of thalidomide, bortezomib and lenalidomide, has improved outcomes; however, elderly patients are more susceptible to side effects[16]. Therefore, this study aims to evaluate the prevalence of neuropathy and to reveal if old age is a risk factor for PN in MM patients. We believe that understanding this potential risk may guide clinicians in developing better preventive as well as symptomatic treatment modalities for PN in this particular population.

To the best of our knowledge, this is among the few, long term analyses evaluating prevalence of peripheral neuropathy that is confirmed with electromyography in older MM patients.

The association between advanced age and PN was evaluated in patients treated with paclitaxel or cisplatin-based regimens for lung or breast cancer by Argyriou et al. The study demonstrated advanced age was not associated with increased incidence and worst severity of PN[17]. Our study has been revealed similar results in a different patient population as well as in a different chemotherapeutic agent group. In this study, peripheral neuropathy rate was 27.2%. While the neuropathy rate was 26.1% in patients 65 and older, it was 28.3% in patients younger than 65. No significant association was found between age and peripheral neuropathy (p=1.00).

Peripheral nerve damage is one of the most significant toxicity of bortezomib. Grades 1 and 2 bortezomib induced PN can occur in 75% and 33% of patients; whereas grades 3 and 4 neurotoxicity may affect in 30% and 18% of patients respectively (12,18,19). The rate of neuropathy in bortezomib group was 24.4 % in our study which is consistent with previously published studies.

PN develops in approximately 50 percent of patients receiving first-line thalidomide treatment for MM[20-22]. Our findings demonstrated neuropathy rate was 36.7 % in thalidomide group that is relatively lower than literature. This might be due to initiating low dose thalidomide treatment and gradually increasing as patient tolerates. It was reported that 30-40% of patients treated with vincristine develop PN[23,24]. The neuropathy rate was 17.6% in our study.

The treatment discontinuation rate has shown 14.1% among the patients and no statistically significant association was found with neuropathy (p=0.330).

The presence of a preexisting neuropathy may also be a risk factor for developing PN with a variety of neurotoxic agents. Diabetes mellitus was the most common risk factor, present in 44% of the patients with polyneuropathy. In our study 16.3% of our patients had history of diabetes, however; the association with diabetes and neuropathy was statistically insignificant.

In survival analysis the estimated median survival time was 27 months in patients with PN, whereas 56 months in patients without PN (p=0.273). The effect of neuropathy, age, gender, performance status and chemotherapy regimen on survival was found statistically insignificant.

The limitations are; it is a single center and retrospective study. On the other hand the strengths of the study are; our sample size is well distributed according to age and PN diagnosis is confirmed with objective methodology using EMG.

In conclusion, this study is among the few, long term analyses evaluating prevalence of PN which is confirmed with electromyography in MM patients. The prevalence of neuropathy was found 27.2%. There was no significant association

between increased age, survival and neuropathy. Evaluating other associations and understanding potential risks may guide us in developing better preventive and treatment modalities for PN in older patients with MM as well as other cancer populations. Therefore well controlled multicenter studies are recommended in the future.

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