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Subgroup Analysis in Multiple Myeloma Patients under Sixty Years: A Single-Center Study

Altmış Yaş Altı Multipl Miyelom Hastalarında Subgrup Analizi: Tek Merkez Çalışma

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ABSTRACT

Introduction: Multiple myeloma (MM) constitutes approximately 10% of hematological malignan-cies with abnormal proliferation of plasma cells, which causes an abnormal increase of monoclonal immunoglobulin light chains. We aim to examine our young myeloma cases' data and compare light chain disease with other subtypes, which are known to have a worse prognosis in all age groups.

Methods: Fifty-five MM patients diagnosed and treated between January 2010 and 2020 under 60 years old, were analyzed retrospectively. Their demographic data, laboratory, treatment subtypes, MM subtypes, CRAB findings (hypercalcemia, renal failure, anemia, and presence of lytic bone lesions), treatment, and responses to the first-line treatment were analyzed. The patients were divided into two groups, the light chain and other myeloma subgroups, and compared statistically.

Results: Seventeen patients were female (30.9%), and 38 were male (69.1%). The median age was 54 (range: 34-59) years. The median duration of follow-up was 30 (range: 3-108) months. The MM sub-types examined were: immunoglobulin G (IgG)/Kappa 13 (23.6%), kappa light chain 10 (18.2%), lambda light chain 10 (18.2%), IgG/Lambda 9 (16.4%), IgA/Lambda 8 (14.5%), and IgA/Kappa 5 (9.1%). There was no significant difference between the two groups except for albumin and calcium values. In the other myeloma subtype group, albumin and calcium values were significantly lower ($p<0.05$) than the light chain group.

Conclusion: The myeloma distribution under the age of 60 was different from that in the general my-eloma population. The light chain was more at the forefront, which appears to be related to lytic le-sions, kidney failure, and amyloidosis. Moreover, albumin, an independent prognostic indicator for myeloma, decreased in the other myeloma subgroup compared with the light chain subgroup. They are first mentioned in the literature in patients under 60 years old.

Keywords: Multiple myeloma, young patients, light chain, albumin, prognosis

ÖZ

Amaç: Multipl miyelom (MM), hematolojik malignitelerin yaklaşık %10'unu oluşturan; monoklonal immünglobulin artışına eşlik eden serbest hafif zincir salınımına neden olan anormal proliferasyon gösteren, malign plazma hücrelerinin oluşturduğu bir hastalıktır. Çalışmamızda, tanı anında 60 yaş altında olan genç miyelom olgularımızın verilerini, retrospektif olarak ortaya koymayı ve kötü prognoza sahip olduğu bilinen hafif zincir hastalığı ile diğer miyelom alt tiplerini karşılaştırmayı amaçladık.

Yöntemler: Ocak 2010 ile Ocak 2020 arasında 60 yaşın altında tanı alarak tedavi edilen elli beş MM hastası retrospektif olarak incelendi. Demografik veriler, laboratuvar parametreleri, tedavi alt tipleri, MM alt tipleri, CRAB bulguları (hiperkalsemi, böbrek yetmezliği, anemi ve litik kemik lezyonlarının varlığı), tedavi ve birinci basamak tedaviye yanıtları analiz edildi. Hastalar hafif zincir ve diğer miyelom alt grupları olarak iki gruba ayrıldı ve istatistiksel olarak aynı başlangıç parametreleri açısından karşılaştırıldı.

Bulgular: On yedisi kadın (%30,9) ve 38'i erkek (%69,1) idi. Ortanca yaş 54 bulundu (aralık: 34-59). Medyan takip süresi 30 aydı (aralık: 3-108). MM alt tipleri incelendiğinde; immünoglobulin G (IgG)/Kappa 13 (%23,6), kappa hafif zincir 10 (%18,2), lambda hafif zincir 10 (%18,2), IgG/Lambda 9 (%16,4), IgA/Lambda 8 (%14,5) ve IgA/Kappa 5 (%9,1) idi. Hafif zincir ve diğer miyelom alt grupları istatistiksel olarak karşılaştırıldı. İki grup arasında albümin ve kalsiyum değerleri dışında anlamlı bir farklılık saptanmadı. Diğer miyelom alt tipi grubunda, albümin ve kalsiyum değerleri hafif zincir grubuna göre anlamlı olarak düşüktü ($p<0,05$).

Sonuç: Çalışmamızda 60 yaşın altındaki miyelom dağılımının, genel miyelom popülasyonu ile aynı olmadığı görülmüş olup; litik lezyon, böbrek yetmezliği ve amiloidoz ile daha çok birliktelik gösteren hafif zincir hastalığı daha fazla görülmüştür. Ayrıca miyelom için bağımsız bir prognositik gösterge olarak görülen albümin, diğer miyelom alt grubunda, hafif zincir grubuna göre anlamlı olarak azalmıştı. Bu bulgular 60 yaş altı miyelom olgularında ilk kez ortaya konulmaktadır.

Anahtar Kelimeler: Multipl miyelom, genç hasta, hafif zincir, albümin, prognoz

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Introduction

Multiple myeloma (MM) constitutes approximately 10% of hematological malignancies. It is a disease caused by malignant plasma cells, which is abnormal proliferation, causing free light chain release accompanying the increase in monoclonal immunoglobulin (Ig) (1). It is possible to say that the data obtained from many publications are seen around 7 in 100,000, and the median age is 65 years old (2-4). Clinical manifestations appear as renal failure, anemia, hypercalcemia, and lytic bone lesions. Although positron emission tomography/computed tomography (PET/CT) is often preferred for the detection of lytic bone lesions, magnetic resonance imaging (MRI), CT, and plain radiographs also contribute to the diagnosis.

The most common MM subtypes are those that show the IgG monotype followed by the IgA monotype (5,6). The light chain subtype is seen at a rate of 15% and appears to have a worse prognosis (6). In the light chain subtype, renal failure, bone lesions, and light chain amyloidosis are more common. It is seen at an earlier age and has a worse prognosis than other subtypes (7,8).

Autologous stem cell transplantation, which forms an integral part of the treatment, also provides the basis for approaching patients in terms of age and sheds light on the definition of "young myeloma." Although there is no exact cut-off to guide treatment determination and demonstration, we see 65 years old as a possible cut-off because of transplantation. Today, the approach to young myeloma, which constitutes approximately 37% of all cases, is particularly critical in planning the treatment process, obtaining an optimal response, and preventing treatment-related toxicities (9).

Our study aims to analyze the data of our young myeloma cases retrospectively and compare light chain disease, which is known to have a worse prognosis in all age groups.

Methods

The data of 55 MM patients under 60 years old who were diagnosed and treated between January 2010 and January 2020 in the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Hematology Outpatient our hospital were analyzed retrospectively. Demographic data of patients (age and gender), hemoglobin, albumin, protein, lactate dehydrogenase (LDH), beta-2 microglobulin, creatinine, calcium, treatment subtypes, and the number of cures applied, and MM subtypes. Also, the preferred detection methods of lytic lesions and rates (PET/CT, CT, and MRI), chromosome analysis at diagnosis and myeloma fluorescence in situ hybridization panel results (if available), CRAB findings at the time of diagnosis (hypercalcemia, renal failure, anemia, and presence of lytic bone lesions), treatment and responses to the first-line treatment, autologous stem cell transplantation rate, duration of follow-up, and final status were analyzed retrospectively. Patients were divided into two groups, the light chain, and other myeloma subgroups, and statistically compared the same baseline parameters. All light chain patients were checked for the presence of IgD and IgE monoclonality.

The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethic Committee and the Ministry of Health (approval number: 2241, date: 27.04.2020). Informed consent was obtained from our patients to publish the presentation.

Statistical Analysis

Average, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov-Smirnov test. An Independent Samples t-test and the Mann-Whitney U test were used in the analysis of independent quantitative data. In the analysis of independent qualitative data, the chi-square test was used. Fisher's exact test was used when chi-square test conditions were not met. The SPSS 26.0 program was used in the analysis.

Results

Data of a total of 55 patients were examined. Seventeen were female (30.9%), and 38 were male (69.1%). The median age was found to be 54 (range: 34-59) years. The median duration of follow-up was 30 (range: 3-108) months.

When MM subtypes are examined, IgG/Kappa was 13 (23.6%), kappa light chain 10 (18.2%), lambda light chain 10 (18.2%), IgG/Lambda 9 (16.4%), IgA/Lambda 8 (14.5%), and the number of patients diagnosed with IgA/Kappa was 5 (9.1%). The number of patients with lytic lesions detected by any imaging method was 43 (78.2%). All patients had a PET/CT at the time of diagnosis; 38 patients had lytic lesions detected by PET/CT (69.1%) (Table 1).

Fifteen (27.3%) of the patients were at the International Staging System (ISS) stage 1, 39 at stage 2 (70.9%), one at stage 3 (1.8%). There were 16 (29.1%) patients with initial renal failure, 21 (38.2%) with anemia, and five patients (9.1%) with hypercalcemia. In the first-line treatment, vincristine-adriamycin-dexamethasone was preferred for 36 patients (65.5%) and bortezomib-cyclophosphamide-dexamethasone (34.5%) for 19 patients. While there were two patients (3.6%) with complete remission after first-line treatment, 12 patients showed progressive disease (21.8%). A total of 45 patients underwent autologous bone marrow transplantation (81.8%). In the final status assessment, 15 patients dropped out (27.3%) (Table 2).

The patients were divided into two groups as light chain and other myeloma subgroups and compared statistically in terms of baseline parameters. Ages, gender distribution, LDH, beta-2 microglobulin, creatinine, hemoglobin value, lytic lesion rate, ISS and Revised-international Staging System stages, renal failure, anemia, and hypercalcemia rate did not differ significantly in the light chain and the other group. In the other myeloma subtype group, albumin and calcium values were significantly lower ($p<0.05$) than the light chain group (Table 3).

Discussion

It is still not possible to talk about curative treatment for MM. Although recent years began a new era with the advent of new immunomodulators and target cell treatments, it also fell short regarding delivering a precise treatment. The main population affected by the disease is older individuals. In this population, mortality is based on chronic and non-myeloma causes, while myeloma is controlled with long-term treatments. Considering the older age of individuals in this age group and their tendency to have comorbidities, it is difficult to talk about curability (10).

Table 1. Demographic data, laboratory results, myeloma subtypes, presence of lytic lesions

		Min-max	Median	Mean ± SD (n, %)
Age		34.0-59.0	54.0	52.1±6.2
Gender	Female	-	-	17 (30.9%)
	Male	-	-	38 (69.1%)
Albumin (g/L)		2.0-5.7	3.8	3.7±0.8
Lactate dehydrogenase (U/L)		104.0-499.0	194.0	198.7±67.3
Beta-2 microglobulin (mg/L)		1.5-43.3	3.1	5.7±7.0
Creatinine (mg/dl)		0.5-6.2	0.9	1.4±1.1
Hemoglobin (g/L)		5.5-15.1	11.3	11.0±2.3
Calcium (mg/dL)		7.9-16.5	9.4	9.7±1.3
Corrected calcium (mg/dL)		7.9-16.3	9.2	9.5±1.3
Number of cycles in first-line treatment		1.0-6.0	2.0	2.9±1.3
Multiple myeloma subtypes	IgG/Kappa	-	-	13 (40%)
	Kappa	-	-	10 (18.2%)
	Lambda	-	-	10 (18.2%)
	IgG/Lambda	-	-	9 (16.4%)
	IgA/Lambda	-	-	8 (14.5%)
	IgA/Kappa	-	-	5 (9.1%)
Presence of lytic lesions	(-)	-	-	12 (21.8%)
	(+)	-	-	43 (78.2%)
PET/CT	(-)	-	-	17 (30.9%)
	(+)	-	-	38 (69.1%)

SD: Standard deviation, Ig: immunoglobulin, PET: positron emission tomography, CT: computed tomography, Min: minimum, Max: maximum

Table 2. ISS scores, CRAB findings (hypercalcemia, renal failure, anemia, and presence of lytic bone lesions), treatment and responses, last status

		Min-max	Median	Mean ± SD (n, %)
ISS	I	-	-	15 (27.3%)
	II	-	-	39 (70.9%)
	III	-	-	1 (1.8%)
R-ISS	I	-	-	14 (25.5%)
	II	-	-	40 (72.7%)
	III	-	-	1 (1.8%)
Renal failure	(-)	-	-	39 (70.9%)
	(+)	-	-	16 (29.1%)
Anemia	(-)	-	-	34 (61.8%)
	(+)	-	-	21 (38.2%)
Hypercalcemia	(-)	-	-	50 (90.9%)
	(+)	-	-	5 (9.1%)
First-line treatment	VAD	-	-	36 (65.5%)
	VCD	-	-	19 (34.5%)
Response	CR	-	-	2 (3.6%)
	PD	-	-	12 (21.8%)
	PR	-	-	9 (16.8%)
	SD	-	-	25 (45.5%)
	VGPR	-	-	6 (10.9%)
	No information	-	-	1 (1.8%)
Stem cell transplantation	(-)	-	-	10 (18.2%)
	(+)	-	-	45 (81.8%)
Follow-up period (month)		3-108	30	36.3±27.8
Drop-out	(+)	-	-	15 (27.3%)
	(-)	-	-	40 (72.7%)

ISS: The International Staging System, R-ISS: Revised-international Staging System, CR: complete response, PD: progressive disease, PR: partial response, SD: stable disease, VGPR: very good partial response, SD: standard deviation, Min: minimum, max: maximum

When speaking to a younger age group, discussions about treatment procedures for an incurable disease warrants a very different approach. Effective treatment requires getting a response to the disease and maintaining it for a meaningful length of time. The preferred treatment subtypes and toxicities explain the essential points in young age myeloma (11-14).

In our study, as in the general population, MM is a male-dominated disease in the patient group under 60. There may be a significant difference regarding the distribution of myeloma subtypes. While the IgG/Kappa myeloma subtype is followed by IgA/Kappa in the general population, in our study, the subtype of IgG/Kappa myeloma is followed by kappa and lambda light chain myeloma. Considering that renal failure, bone lesions, and AL amyloidosis are seen in the light chain myeloma, it seems quite possible to expect these three parameters to be prominent under 60. However, in our study, no significant difference was observed in the group under 60 years of age regarding renal insufficiency at the time of diagnosis. As mentioned earlier, considering the literature, there was significantly more involvement of light chain

Table 3. Statistical analysis of parameters

		Light chain subgroup		Other subgroup		p	
		Mean ± SD (n, %)	Median	Mean ± SD (n, %)	Median		
Age		53.5±5.5	55.0	51.4±6.5	54.0	0.232	m
Gender	Female	8 (40%)	-	9 (25.7%)	-	0.270	X^2
	Male	12 (60%)	-	26 (74.3%)	-		
Albumin (g/L)		4.0±0.8	4.2	3.5±0.7	3.4	0.019	t
Lactate dehydrogenase (U/L)		200.3±54.5	195.5	197.8±74.3	188.0	0.898	t
Beta-2 microglobulin (mg/L)		4.7±4.2	2.6	6.3±8.2	3.85	0.164	m
Creatinine (mg/dl)		1.6±1.3	1.1	1.2±0.9	0.89	0.426	m
Hemoglobin (g/L)		11.4±2.2	11.6	10.8±2.3	11.1	0.375	t
Calcium (mg/dL)		10.2±2.0	9.9	9.3±0.7	9.2	0.043	m
Corrected calcium (mg/dL)		9.8±1.9	9.3	9.4±0.8	9.2	0.793	m
Number of cycles in first-line treatment		3.0±1.3	3.0	2.8±1.4	2.0	0.530	m
Presence of lytic lesions	(-)	2 (10%)	-	10 (28.6%)	-	0.109	X^2
	(+)	18 (90%)	-	25 (71.4%)	-		
PET/CT	(-)	5 (25%)	-	12 (34.3%)	-	0.473	X^2
	(+)	15 (75%)	-	23 (65.7%)	-		
ISS	I	6 (30%)	-	9 (25.7%)	-	0.977	X^2
	II	14 (70%)	-	25 (71.4%)	-		
	III	0 (0%)	-	1 (2.9%)	-		
R-ISS	I	6 (30%)	-	8 (22.9%)	-	0.792	X^2
	II	14 (70%)	-	26 (74.2%)	-		
	III	0 (0%)	-	1 (2.9%)	-		
Renal failure	(-)	12 (60%)	-	27 (77.1%)	-	0.178	X^2
	(+)	8 (40%)	-	8 (29.9%)	-		
Anemia	(-)	13 (65%)	-	21 (60%)	-	0.714	X^2
	(+)	7 (35%)	-	14 (40%)	-		
Hypercalcemia	(-)	17 (85%)	-	33 (94.3%)	-	0.342	X^2
	(+)	3 (15%)	-	2 (5.7%)	-		
First-line treatment	VAD	9 (45%)	-	27 (77.1%)	-	0.016	X^2
	VCD	11 (55%)	-	8 (22.9%)	-		
Stem cell transplantation	(-)	4 (20%)	-	6 (17.1%)	-	0.899	X^2
	(+)	16 (80%)	-	29 (82.9%)	-		
Follow-up period (month)		41.4±27.9	38.5	33.4±27.6	28.0	0.308	t
Drop-out	(-)	17 (85%)	-	23 (65.6%)	-	0.122	X^2
	(+)	3 (15%)	-	12 (34.4%)	-		

x,t,m: Mann-Whitney U test, X^2: chi-square test, t: Independent Samples t-test, PET: positron emission tomography, CT: computed tomography, SD: standard deviation, ISS: The International Staging System, R-ISS: Revised-international Staging System, VAD: vincristine-adriamycin-dexamethasone, VCD: bortezomib-cyclophosphamide-dexamethasone

patients in lytic lesions. In contrast, no significant difference was found in our study with light chain myeloma.

In our study, the initial calcium and albumin values were significantly lower in the other myeloma subtypes compared with the light chain group. However, there was no significant difference in the corrected calcium levels. Serum albumin level is defined as an independent risk factor in MM. In a 2009 study (15), patients diagnosed with 373 MM and their data were analyzed. While the patient group with serum albumin 3.5 and below were older, they had lower hemoglobin levels and worse performance status than other groups. Also, beta-2 microglobulin, serum M protein, and the bone marrow plasma cell ratio were higher in this group. In our study, the albumin level was significantly lower in the other myeloma subtypes group than the light chain group. Considering that light chain patients have a worse disease course in the general population, it should be emphasized that this finding is new in the patient group under 60 years old.

In the first treatment series, the combination of bortezomib-adriamycin-dexamethasone was frequently preferred in our case series. Until about three years ago, the use of this combination was mandatory in primary care in accordance with the health system legislation in our country. Today, we use combinations of cyclophosphamide or lenalidomide and bortezomib dexamethasone as the first-line therapy. Reports in the literature also focus on combinations of lenalidomide bortezomib and autologous stem cell transplantation (9).

Conclusion

Our study contains important results concerning MM subgroup data and clinical features in the group under 60 years old. The disease subtype distribution under the age of 60 different from the general myeloma population, and the light chain was more at the forefront. Albumin decreased in the other myeloma subgroup compared with the light chain group. This investigation is the first in the literature to study patients under 60 years old, regarding data revealed by albumin, which is seen as an independent prognostic indicator for myeloma. However, the comparison was not possible concerning the group's treatment heterogeneity and the number of patients.

Acknowledgment

We respectfully remember all the colleagues we lost in the COVID-19.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethic Committee and the Ministry of Health (approval number: 2241, date: 27.04.2020).

Informed Consent: Informed consent was obtained from our patients to publish the presentation.

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