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Multiple Myeloma; Experience of a Center

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Özet:

Amaç : Multıple myelom(MM) tanısı konulmuş olan hastaların tanı anındaki demografik özellikleri, laboratuvar parametreleri, verilen tedavileri ve tedavi yanıtları toplumlar arası farklılık göstermektedir. Multple myelom hastalarının bu verilerini araştırmayı ve literatür verileriyle karşılaştırmayı hedefledik.

Materyal Metot : Bu çalışmada 1 Ocak 2010-31 Ocak 2019 tarihleri arasında ..... Üniversitesi tıp fakültesi iç hastalıkları hematoloji kliniğinde MM tanısı konulmuş 272 hastanın verileri retrospektif olarak incelendi. Çalışmaya alınan hastaların tanı anındaki genel özellikleri, laboratuvar değerleri, tedavi seçenekleri, tedavi yanıtları, ortalama ve ortanca sağkalım süreleri ve mortalite nedenleri araştırıldı.

Bulgular: Multıple myelom hastalarımızın alt tip analizlerinde hastaların 124'ü(%45,6) ıgG, 50'si(%18,4) ıgA, 59'u(%21,7) hafif zincir, 21'i(%7,7) plazmasitom, 4'ü(%1,5) ıgM, 3'ü(%1,1) plazma hücre lösemisi, 11'i(%4) de nonsekretuvar myelom olarak bulundu. 77 hastaya otolog hematopoetik kök hücre nakli (OHKHN) yapıldı. OHKHN yapılan hastalarda ortalama yaşam süresi 68 ay iken OHKHN yapılmayan hastalarda bu süre 42 ay olarak tespit edildi ($p<0,001$). En sık mortalite sebeblerini enfeksiyonlar (%55), tromboembolik olaylar (%22), hemorajik kompikasyonlar ve hastaların komorbid durumları (%22) oluşturdu.

Sonuç: Myelom tanımlayıcı olayların oranları, tedavi yanıt oranları, sağkalım süreleri, OHKHN yapılan hastalardaki sağkalım süreleri ve mortalite nedenleri literatür verileriyle benzer bulundu. Tedavi yanıt oranları ve ortalama sağkalım sürelerinin yeni ajanların çıkmasıyla arttığını görmekteyiz.

Anahtar Kelimeler: *Myelom, New agents, Transplantation*

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Abstract:
Objective: Demographic characteristics, laboratory parameters, applied treatments, and treatment responses of patients diagnosed with multiple myeloma (MM) at the time of diagnosis vary between communities. We aimed to investigate this data of Multiple Myeloma patients and compare it with literature data.
Material Method: In this study, we retrospectively examined data of 272 patients diagnosed with MM between January 1st, 2010, and January 31st, 2019 in ..... University Faculty of Medicine Internal Medicine Hematology Clinic. At the time of diagnosis, general characteristics, laboratory values, treatment options, treatment responses, mean and median survival times, and causes of mortality of the participated patients in the study were investigated.
Results: We found that 124 (45.6%) patients had IgG, 50 patients had (18.4%) ıgA, 59 patients had (21.7%) light chain, 21 patients had (7.7%) plasmacytoma, four patients had (1.5%) ıgM, three patients had (1.1%) plasma cell leukemia, and 11 patients had (4%) non-secretory myeloma. 77 patients underwent autologous hematopoietic stem cell transplantation (AHSCT). The average life expectancy in patients with AHSCTwas 68 months, while in patients without AHSCT, this period was determined as 42 months (p<0.001).
Conclusion: We see that treatment response rates and average survival times increase with the introduction of new agents.

Key words: *Myelom, New agents, Transplantation*

Introduction

Multiple myeloma (MM) is a hematological disorder characterized by the proliferation of malignant plasma cells in the bone marrow. Plasma cells produce abnormal monoclonal paraprotein and/or immunoglobulin light chains, causing organ damage[1]. At the time of diagnosis, 20% of patients experience kidney failure, which is also of prognostic importance[2]. Anemia (hb<10 g/dl) occurs in 40-72% of patients[3]. 66% of patients with multiple myeloma have a bone event (osteolytic bone lesions, bone fractures, and osteoporosis). The average life expectancy with traditional chemotherapy regimens is 3-4 years, while with autologous hematopoietic stem cell transplantation, this period has increased to 5-7 years. The life expectancy of 5 years is 46%[4]. Immune paralysis is the main cause of frequent and severe infections in myeloma. It is also the biggest cause of mortality[5]. Other causes of mortality are treatment-related toxicity and thrombosis, bleeding, and amyloidosis in patients diagnosed with multiple myeloma[3,5].

The objective of this study conducted on 272 patients diagnosed with MM at adult hematology clinic is to investigate the demographic characteristics of patients such as age, gender at the time of diagnosis, their hemogram and biochemical parameters, presence of bone cases, whether they have or have not received radiation therapy, which type of myeloma was diagnosed, whether AHSCT

performed or not, patients' mean and median survival time diagnosed with multiple myeloma and mortality causes.

Materials and Methods

This study included 272 patients older than 18 who were diagnosed with MM between January 1st, 2010 and January 31st, 2019 in Dicle University Faculty of Medicine Internal Medicine Hematology Clinic and whose data can be accessed.

The 2010 International Myeloma Working Group (IMWG) diagnostic criteria were applied to patients diagnosed before 2015, and the updated IMWG diagnostic criteria as of 2014 were applied to patients diagnosed in 2015 and after. Demographic characteristics of patients diagnosed with MM at the time of diagnosis were investigated, their values of hemoglobin (Hb), platelet (plt), white blood cell (WBC), urea, creatinine (cr), calcium (ca), total protein, globulin, the presence of bone cases, myeloma subtypes, treatment responses, life expectancy, and causes of mortality were investigated using the hospital system.

In this study, the prevalence of the disease, the age, the female-male ratio, the rates of events descriptive at myeloma diagnosis, except for anemia, and the presence of bi-cytopenia, pancytopenia; their total protein and globulin values, the sub-type of myeloma, the sequence of their treatment, causes of mortality, and survival were evaluated.

Comparing the life expectancy of patients with and without AHSCT, the treatment response rates in stages and the causes of mortality were reviewed.

The Dicle University Faculty approved this thesis of Medicine Non-interventional Clinical Research Ethics Committee's Decision No. 196 dated 06.06.2018.

Statistical Analysis: Statistical analysis of the results obtained in the study was performed using the statistical software package SPSS (Statistical Package for the Social Sciences) 18.0. Descriptive statistics amongst the continuous variables focused on were expressed as mean ± standard deviation, minimum and maximum value, while categorical variables were expressed as numbers and percentages. Chi-square test was also used in the analysis of categorical variables (such as gender, bone involvement, renal failure, hypercalcemia, anemia). Overall survival, intra-group survival, and 5-year life expectancy were investigated using the Kaplan-Meier test. In these tests, the value of p (probability) less than 0.05 was considered to be statistically significant.

Result

The median age of 272 patients admitted to ..... University Hospital and diagnosed with MM was 64 (24-94), and the average age of disease incidence was 62. Out of the patients, 159 (58.5%) were male, and 113 (41.5%) were female. The number of patients under 40 years of age was 13 (4.8%), the number of patients over 65 years of age was 125 (45.9%), the number of patients between 40-65 years of age was 134 (49.3%), and the ratio of men and women was 1,4/1 (Table 1).

Table 1: Age and Gender distributions of patients at the time of admission

Number of male patients	159(%58,5)
Number of female patients	113(%41,5)
Male / female ratio	1,4/1
Number of patients under 40	13(%4,8)
Number of patients aged between 40-65	134(%49,3)
Number of patients over 65	125(%45,9)
Average age of patients	62±11,6
Average age of male patients	59,9±11,7
Average age of female patients	65,1±10,9
Median age (min-max)	64(24-94)

Lab values at the time of diagnosis were analyzed. 121 (44.5%) patients with Hb<10 gr/dl, 37 (13.6%) with wbc<4.5 10^3/uL and 30 (11%) with plt<100 10^3/uL were determined. 46 (16.9%) patients with calcium>11 mg/dl and 54 (19.9%) patients with creatinine>2 mg/dl were determined.

172 (63%) of patients were admitted with a bone case (lytic lesion, pathological fracture, osteoporosis). The most commonly seen bone involvement was vertebral involvement with 111 patients. 100 patients had no bone involvement, while 26 (9.6%) patients had bone involvement in more than one location. 65 of 172 patients with bone involvement underwent radiation therapy in addition to chemotherapy.

124 (45.6%) of the patients had IgG, 50 (18.4%) of the patients had IgA, 59 (21.7%) of the patients had a light chain, 21 (7.7%) of the patients had plasmacytoma, 4 (1.5%) of the patients had IgM, 3 (1.1%) of the patients had plasma cell leukemia (PCL), and 11 (4%) of the patients had non-secretory myeloma when multiple myeloma subtype analysis was performed.

In patients who were not treated employing AHSCT, the median life span was 35 months (standard deviation:2,3 CI:30-400), while in the group of patients who had AHSCT, the median life span was not found ($p<0.001$). In the AHSCT group, the median survival time was significantly longer than in the group without AHSCT. The overall 5-year survival rate of patients was found to be 35%. The best 5-year survival rate was 63% in patients with AHSCT, while this rate was 24% in patients without AHSCT.

In survival analyses according to MM subgroups, the best median survival was found in IgG-type myeloma, while the worst survival was found in plasma cell leukemia (Table-2).

Table 2. Median and Average survival times by MM subtype

subtype	median survival time	95% CI (confidence interval)	average survival-time	95% CI (confidence interval)
Ig G	52,5±5,9	40,9-64,1	54,2±4,4	45,6-62,9
Ig A	40,2±9,4	21,7-58,7	41,2±4,4	32,5-49,9
Kappa	48,7±17	15,4-82,1	43,3±6,4	30,6-55,4
Lambda	42,4±14,3	14,2-70,6	45,8±6	34-57,7
Plasmacytoma	40,8±3,4	34,1-47,6	50,4±8,3	34,2-66,7
Ig M	49,1±16,7	0-76	49,1±16,7	16,2-82
PCL	7,3±4,1	0-15,4	8,1±2,9	2,3-13,8
Non-secretory	44,2±7,8	28,9-59,5	44,1±9	26,4-61,8

In our study, 107 of 272 patients died. The most common causes of death were infection, thrombotic and hemorrhagic complications, and patients' existing comorbid conditions. When we reviewed co-morbid conditions, 5 patients had simultaneous advanced heart failure (EF<35%), 3 patients had amyloidosis and heart failure, and 6 patients had COPD.

DISCUSSION

Multiple myeloma is known as an advanced age disease, and it is relatively less common in young people and has male dominance[6]. In a study involving patients from the United States, Germany, Canada, and the United Kingdom, the average age of occurrence was 67, and the ratio of men and women was 1,5/1[7]. In our study, 272 patients had a median age of 64(24-94) and an average age of 62. Out of the patients, 159 (58.5%) were men and 113 (41.5%) were women, the male/female ratio was high in old age and men, similar to 1,4/1 studies.

A multi-center study conducted in South Korea showed a bone involvement rate of 60.2%, anemia rate of 60.7%, and acute kidney damage rate of 23.4%, hypercalcemia rate of 16.7%[8]. The rates of hypercalcemia (16.9%), acute kidney injury (19.9%), bone involvement (63%), and anemia (78.7%) observed in our patients were similar to this study.

In a study, the most common subtype of myeloma was IgG and then light chain and IgA, respectively, while the least observed ones were IgD and non-secretory type of myeloma[9]. When the subtype analysis was performed, IgG 45.6%, IgA 18.4%, light chain 21.7%, plasmacytoma 7.7%, IgM 1.5%, plasma cell leukemia 1.1%, and non-secretory myeloma 4% were found. Despite

high-dose chemotherapy and bone marrow transplantation in plasma cell leukemia, response rates are still meager, and the prognosis is poor[10]. In our study, the lowest median life expectancy (7.3±4.1 months; CI:0-15,4) the highest median life expectancy (52.5±5.9; CI: 40.9-64.1) was observed in plasma cell leukemia in the IgG subtype.

The total response rate (partial response, minimal response, excellent partial response, stable disease) in VCD (bortezomib, cyclophosphamide, dexamethasone) treatment ranges from 80-90%, while the total response rate ranges from 46-52%[11]. In our study, the total response rate of patients receiving VCD treatment in primary care was found as 58.5%.

In a study conducted by Emilie et al., the AHSCT treatment response was 73%[12]. This rate was 76% in our study. The average and median life expectancy in patients with AHSCT was significantly higher than in the group without AHSCT. 5-year survival rate was 63% in patients with AHSCT, while this rate was 24% in patients without AHSCT.

Conclusion: The median and average survival times were extended for the newly diagnosed MM patient with all the improvements in treatment. AHSCT is seen as the most effective treatment option[13]. For this reason, it is crucial to evaluate the MM patient for AHSCT and apply treatment in this direction. Bone involvement is the most common form of admission. For this reason, it is essential to bring MM to mind in patients who have complaints of bone pain or musculoskeletal system. Mortality is most commonly associated with infectious and thrombosis, and it is highly vital that administering anticoagulant or antiagregant and prophylactic antiviral, antifungal and antibacterial treatments to patients with risk factors at all stages of treatment and follow-up.

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