Original Article

Uric Acid and Multiple Myeloma, Unexplored Association

Ürik Asit ve Multiple Miyeloma, Keşfedilmemiş İlişki

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ABSTRACT

Introduction: Multiple Myeloma (MM) is a common hematological malignancy and various factors affect survival. Uric acid (UA) is an easily and quickly accessible laboratory test. UA has been found to affect prognosis and survival in many hematological diseases and its impact on myeloma is not widely investigated.

Methods: Our retrospective study includes 106 MM patients between 2014 and 2021. The influence of UA level at diagnosis on treatment outcomes and survival of patients who received autologous stem cell transplantation (ASCT) was investigated.

Results: The mean UA at diagnosis was 6.05 mg/dL, and 38.7% of our cohort relapsed after a median of 30 months of follow-up, with 22.7% dead. In survival analysis, the level of UA did not significantly differ in both progression-free survival (PFS) and overall survival (OS) (HR, 1.067; 95% CI, 0.947-1.202; p=0.290, HR, 0.941; 95% CI, 0.791-1.121; p=0.497, respectively).

Discussion and Conclusion: In our study, regardless of the cut-off value for the UA level at the time of diagnosis, the UA level had no impact on PFS or OS in MM patients who received ASCT.

Keywords: Hyperuricemia, Plasma Cell Disorders, Hematopoietic Stem Cell Transplantation, Prognosis, International Scoring System

ÖZET

Giriş ve Amaç: Multipl Miyelom (MM) sık görülen bir hematolojik malignitedir ve çeşitli faktörler sağkalımı etkiler. Ürik asit (ÜA), kolay ve hızlı erişilebilir bir laboratuvar testidir. ÜA'nın birçok hematolojik hastalıkta prognozu ve sağkalımı etkilediği bulunmuştur ve miyelom üzerindeki etkisi geniş çapta araştırılmamıştır.

Yöntem ve Gereçler: Retrospektif çalışmamız 2014-2021 yılları arasında 106 MM hastasını içermektedir. Otolog kök hücre nakli (OKHN) uygulanan hastaların tanı anındaki ÜA düzeyinin tedavi sonuçları ve sağ kalım üzerine etkisi araştırılmıştır.

Bulgular: Tanı anında ortalama ÜA 6.05 mg/dL idi ve kohortumuzun %38.7'si medyan 30 aylık takipten sonra nüks etti ve %22,7'si hayatını kaybetmişti. Sağ kalım analizinde, ÜA seviyesi hem hastalıksız sağ kalım (PFS) hem de genel sağ kalım (OS) açısından önemli ölçüde farklı değildi (HR, 1.067; %95 GA, 0.947-1.202; p=0.290, HR, 0.941; %95 CI, 0.791-1.121; p=0.497, sırasıyla).

Tartışma ve Sonuç: Çalışmamızda, OKHN uygulanan MM hastalarında, tanı anındaki ÜA düzeyi için cut-off değeri ne olursa olsun, ÜA düzeyinin PFS veya OS üzerinde etkisi yoktu.

Anahtar Kelimeler: Hiperürisemi, Plazma Hücre Bozuklukları, Hematopoetik Kök Hücre Nakli, Prognoz, Uluslararası Skorlama Sistemi

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Introduction

Multiple Myeloma (MM) constitutes 1% of all cancers and approximately 10% of hematological malignancies [1]. It is an incurable disease and approximately 140,000 new cases are encountered worldwide each year. Despite advances in treatments, the mean overall survival was found to be 5.2 years [2,3]. Disease stage, cytogenetic abnormalities, and response to treatment are among the most important factors affecting survival [4]. The International Scoring System (ISS-including albumin and beta-2 micro-globulin measurements), and the Revised International Scoring System (R-ISS-which is formed by adding cytogenetic tests and lactate dehydrogenase [LDH] to the ISS, have become more popular in recent years), and are used in disease staging. According to the International Myeloma Study Group (IMWG), after a mean follow-up of 46 months, 5-year overall survival rates of R-ISS 1, R-ISS 2, and R-ISS 3 are 82%, 62%, and up to 40%, respectively [5,6]. Among the other factors influencing survival, response to therapy is related to the depth of response and response time, and it has been demonstrated to have a significant impact on disease prognosis [7,8].

Uric acid (UA), which is generated when purine nucleotides are degraded, is a proinflammatory marker in epidemiological research, and some studies suggest it may be a hematological marker [9,10]. Also, adverse effects of UA on prognosis and complications in various hematological diseases and hematopoietic cell transplantation (HCT) have been detected [11-14]. Despite the importance of UA in hematological diseases, very limited information was obtained in our literature review regarding the UA level and the course of the disease in MM patients. One of these studies, which investigated the etiology of MM and oxidative stress, found that the UA level in myeloma patients was not significantly higher than in the healthy control group [15]. In contrast to this study, another investigation found that patients with high UA levels had a worse disease stage, laboratory parameters, and survival [16].

In terms of disease follow-up, simple and rapid tests that can predict treatment response and prognosis in hematological disorders are crucial. Our goal is to see how the UA level at the time of diagnosis affects treatment outcomes and survival in MM patients who had autologous stem cell transplantation.

Methods

This study was designed as a retrospective observational cross-sectional study. Electronic media and archive files of MM patients who were admitted to Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Hematology Clinic between 2014 and 2021 were scanned. The study included patients with MM who were between the ages of 18 and 75 and were receiving an autologous transplant. Patients who did not have UA measurement at the time of diagnosis, who underwent second autologous and allogeneic cell transp-lantation, and who used melphalan 140 mg/m^2 as a conditioning regimen in auto-logous stem cell transplantation were excluded from the study. This study was conducted under ethical principles in accordance with the Declaration of Helsinki. Local ethics committee approval was obtained (Date:23/12/2021 Number: 2021-12/24).

The diagnosis of MM was made according to the IMWG-2014 criteria [1]. Patients' demo-graphic information, Eastern Cooperative Oncology Group (ECOG) performance score, UA level, myeloma-related parameters (hemoglobin, calcium, creatinine, LDH, ISS, R-ISS), and hematopoietic cell trans-plantation-specific comorbidity index (HCT-CI) data were all collected. Definitions were made for ISS and R-ISS in accordance with IMWG's criteria in 2005 and 2015, respectively [5,6]. HCT-CI was calculated according to the

Table 1. Demographic features of the patients

Parameters	N=106 (100%)
Age (median, min-max)	57,5 (28-75)
Gender (M/F)	61 (57.5%) / 45 (42.5%)
ECOG (0/ ≥1)	57 (53.8%) / 49 (46.2%)
Comorbidity (present)	30 (28.3%)
MM subtype	
Heavy chain	78 (73.6%)
Light chain	25 (23.6%)
Non-secretory	3 (2.8%)
International Scoring System Stage	
ISS I	39 (36.8%)
ISS II	38 (35.8%)
ISS III	29 (27.4%)
Revised International Scoring System Stage	
R-ISS I	36 (34%)
R-ISS II	45 (42.5%)
R-ISS III	21 (19.8%)
N/A	4 (3.8%)
Laboratory	
Hb (g/dL)	11.55 (6.53-16.3)
Uric acid (mg/dL)	6.05 (1.8-15.5)
Creatinine (mg/dL)	0.88 (0.34-6.9)
Calcium (mg/dL)	9.6 (8.1-16.6)
LDH (U/L)	190 (80-829)

M, Male; F, Female; ECOG, Eastern Cooperative Oncology Group; MM, Multiple Myeloma; ISS, International Staging System; R-ISS, Revised International Staging System; Hb, hemoglobin; LDH, Lactate dehydrogenase

Table 2. Treatment details

Parameters	N=106 (100%)
Induction Chemotherapy	
VCD	99 (93.4%)
VTD	4 (3.8)
VCD + VRD	3 (2.8)
Radiotherapy (applied)	10 (9.4%)
Pre-ASCT Response	
CR	51 (48.1%)
VGPR	25 (23.6%)
PR	28 (26.4%)
SD	2 (1.9%)
HCT-CI score (0 -1 / ≥ 2)	90(84.9%) / 16 (15.1%)
Post-ASCT Response	
CR	65 (61.3%)
VGPR	16(15.1%)
PR	18 (17%)
N/A	7 (6.6 %)
Median follow up (months) (median,min max)	30 (8-75)
Relapse	41(38.7%)
Mortality	24 (22.7%)

VCD, bortezomib-cyclophosphamide-dexamethasone; VTD, bortezomib-thalidomide –dexamethasone; VRD, bortezomib-lenalidomide-dexamethasone;
CR, complete response; VGPR, very good partial response; PR, partial response;
SD, stable disease; N/A, not applicable

definitions of Sorror et al. in 2005 [17]. Data on treatment responses before and three months after autologous stem cell transplantation, progression-free survival (PFS), and overall survival (OS) were collected. PFS was defined as the latest date after the beginning of therapy when there was no evidence of recurrence, death from any cause, or no recurrence. OS was defined as the date from the start of treatment until death from any cause or the last date the patient was known to be alive.

Statistical Analysis

Analyzes were performed with SPSS Software (Version 26.0 Armonk, NY). Descriptive statistics were used to summarize the data. Categorical data were expressed as ratios, and numerical data as median and mean ± standard deviation. Kolmogorov Smirnov test was used as the normal distribution test. Survival analysis Kaplan Meier test was performed. Factors affecting survival were evaluated with log-rank. Factors predicting survival with Cox regression analysis were first analyzed univariate and factors with $p<0.3$ were included in the multiple analysis. $P<0.05$ was considered statistically significant.

Results

A total of 215 patients were screened in the study, 109 of them were excluded and a total of 106 patients were included.

The patients in the study had a median age of 57.5 (ranges:28-75), and 57.5 % of them were male. In terms of performance score, 53.8%

Table 3. Factors influencing overall survival

	Univariate Analysis		Multivariate Analysis	
Factors	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
Age	1.016 (0.953-1.083)	0.626		
Gender (ref female)	1.382 (0.617-3.092)	0.432		
ECOG	1.680(0.791-3.569)	0.177	1.645 (0.750-3.611)	0.214
Uric Acid	0.941 (0.791-1.121)	0.497		
LDH	1.003 (1.000-1.006)	0.021	1.002 (1.00-1.005)	0.065
Hb	1.005 (0.838-1.205)	0.958		
ISS	1.267 (0.774-2.075)	0.346		
R-ISS	1.309 (0.772-2.220)	0.318		
HCT-CI score	1.409 (0.983-2.020)	0.062	1.348 (0.931-1.952)	0.114

**p<0.05 was regarded as statistically significant. Factors with p<0.3 in univariate analysis were regarded as eligible for multivariate analysis.*
ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; Hb, hemoglobin; ISS, International Staging System; R-ISS, Revised International Staging System; HCT-CI score, Hematopoietic cell transplantation-specific comorbidity index

Table 4. Factors influencing progression-free survival

	Univariate Analysis		Multivariate Analysis	
Factors	Hazard Ratio (95% CI)	*P* value	Hazard Ratio (95% CI)	*P* value
Age	1.012 (0.970-1.055)	0.583		
Gender (ref female)	1.160 (0.841-1.599)	0.367		
ECOG	1.492 (0.839-2.653)	0.173	1.430 (0.784-2.608)	0.243
Uric Acid	1.067 (0.947-1.202)	0.290	1.032 (0.909-1.172)	0.623
LDH	1 (0.997-1.003)	0.775		
Hb	0.933 (0.810-1.074)	0.334		
ISS	1.298 (0.880-1.917)	0.190	1.245 (0.805-1.924)	0.325
R-ISS	1.124 (0.748-1.689)	0.573		
HCT-CI score	1.168 (0.894-1.525)	0.255	1.188 (0.902-1.564)	0.220

**p<0.05 was regarded as statistically significant. Factors with p<0.3 in univariate analysis were regarded as eligible for multivariate analysis.*
ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; Hb, hemoglobin; ISS, International Staging System; R-ISS, Revised International Staging System; HCT-CI score, Hematopoietic cell transplantation-specific comorbidity index

were ECOG 0 and 28.3% had comorbidities. The mean UA at the time of diagnosis was 6.05 mg/dL, and Table 1 summarizes the patients' demographic data, MM subtype information, ISS, R-ISS, and laboratory data.

VCD (bortezomib, cyclophosphamide, dexamethasone) chemotherapy was used as induction chemotherapy in 93% of the patients, and complete response (CR) was achieved in 51% of the patients before autologous transplantation. CR was seen at a rate of 65% in the third month of post-transplant response evaluation. The median follow-up time was 30 months, with a recurrence rate of 38.7% and a mortality rate of 22.7%. Treatment details are summarized in Table 2.

In the analysis of the OS effect performed, it was determined that the UA level had no significant impact on OS (HR, 0.941; 95% CI, 0.791-1.121; p=0.497). Only the level of LDH on OS showed a significant difference in univariate analysis (HR, 1.003; 95% CI, 1.000-1.006; p=0.021); however, this

difference was lost in multivariate analysis (HR, 1.002; 95% CI, 1.000-1.005; p=0.065). There was no significant difference in PFS (HR, 1.067; 95% CI, 0.947-1.202; p=0.290) in the analysis of the effect of UA level, and no factor that showed a significant difference in PFS was found in the statistical analysis (HR, 1.067; 95% CI, 0.947-1.202; p=0.290). Survival analyzes are summarized in Tables 3-4.

Discussion and Conclusion

In our study, we found that the UA value at the time of diagnosis had no effect on progression-free survival or overall survival in our group of MM patients who had VCD induction treatment and consolidation treatment with ASCT in the follow-up.

Although there is previous literature on the negative prognostic feature of UA level at diagnosis for different hematological malignancies, there are very limited and contradictory results on the relationship between UA level and prognosis in MM patients [13,18]. In one of the few studies, Kohsari et al. found that in stage-1 MM patients, the UA level did not increase when compared to the control group [15]. On the other hand, a separate study evaluating the prognosis relationship of UA with 94 MM patients with a sample size similar to ours found that the group with a high UA level (cut-off value; 455.4 mol/L [equivalent to 7.6 mg/dL]) had negative prognosis factors such as advanced disease, high cytogenetic risk, and overall survival decreased, suggesting that it could be a potential biomarker in predicting MM prognosis [16]. However, in our study, we observed that UA level had no effect on PFS or OS in MM patients (HR, 1.067; 95% CI, 0.947-1.202; p=0.290), and (HR, 0.941; 95% CI, 0.791-1.121; p=0.497), respectively. Except for LDH, which had a significant impact on OS in univariate analysis (HR, 1.003; 95% CI, 1.000-1.006; p=0.021), no factor (including ISS and R-ISS) was shown to affect survival in our analysis. This might be due to the small sample size resulting from the exclusion of patients whose uric acid level was not reached at the time of diagnosis, as well as the use of ASCT in patients who achieved a certain level of response.

In our evaluation of the literature, we discovered no studies examining the diagnosis or pre-transplant UA level in patients who underwent ASCT, even though there are many studies examining the consequences of allogeneic stem cell transplantation (allo-SCT). Among these studies, the European Society for Blood and Marrow Transplantation (EBMT) Transplant Complication Working Party published a study in 2020 that divided pre-transplant UA levels in allo-SCT patients into low and high (cut-off value: 4.3mg/dL) cohorts and investigated the impact on the transplant. In the cohort with high UA levels, there was a decrease in PFS and OS, and a significant increase in non-relapse mortality (NRM) and relapse after alloSCT [19]. This may be because of the unfavorable effect of high UA levels on humoral and cellular immunity on the graft in allogeneic transplants [20]. Even though all of our patients had ASCT, we were unable to identify an effect of UA level on PFS and OS at any cut-off value in our study. While UA level does not affect prognosis in patients who have undergone ASCT, UA has a prognostic effect in patients who have undergone allo-SCT, which may be due to the immune system's active role in allo-transplantation patients.

The retrospective design of our study is one of its main limitations. Other than that, to create a homogenous study population in our study, we used very stringent inclusion criteria, and patients who did not have a UA level at the time of diagnosis were also excluded. As a consequence, only 106 patients were included in the study out of 215 screened patients, making our sample group smaller. Both the

negative statistical results of the decrease in our sample group and the selection of all patients in our group from the patients who underwent ASCT had a negative impact on our study's ability to demonstrate the predictive effect of UA. Therefore, while our study provides information on the prognostic value of UA, particularly in MM patients who received ASCT, generalizing it to all MM patients may not be appropriate.

In conclusion, we found that the UA level at the time of diagnosis had no influence on PFS and OS in MM patients who had ASCT in our study. Even though UA is a commonly used test in hematological malignancies for information such as inflammation and tumor burden in current practice, we were unable to demonstrate its influence on the prognosis of MM patients in our study.

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