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Original Article / Özgün Araştırma

The Value of International Staging System in Predicting Survival of Multiple Myeloma Patients With Renal Failure

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Abstract

Objectives: At the time of diagnosis, 20 to 30% of multiple myeloma (MM) patients have renal failure. International Staging System (ISS) is based on 2 variables: serum levels of albumin and beta 2-microglobulin (B2M). Serum B2M level increases in patients with renal failure. This means that the elevated serum level of B2M is not always correlated with tumor burden in MM patients who have renal failure. Therefore, these patients may have further ISS stages than they really have. In this study, we aim to evaluate the success of ISS in predicting survival in MM patients with renal failure.

Method: The data of 172 MM patients that underwent autologous stem cell transplantation (ASCT) at our center were retrospectively analyzed. The patients were divided into 5 renal function stages according to the Renal Disease Quality Classification of the National Kidney Foundation.

Results: Overall survival (OS) after ASCT was found 21 months in ISS1 patients, 20 months in ISS2 patients, and 18 months in ISS3 patients. OS in stage 0-1 patients was 18 months, it was 30 months in stage 2-3-4-5 patients. There was no statistically significant difference regarding OS between patients with renal failure and normal renal function in all ISS stages.

Conclusion: Our data reveals that the significance of ISS to predict overall survival is independent from renal failure.

Keywords: Multipl myeloma, renal failure, international staging system

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Renal Yetmezliği Olan Multipl Myelom Hastalarında Uluslararası Evreleme Sisteminin Sağkalımı Göstermedeki Değeri

Öz

Giriş: Tanı anında Multipl miyelom (MM) hastalarının % 20 ila % 30'u böbrek yetmezliğine sahiptir. Uluslararası Evreleme Sistemi (ISS) 2 değişkene dayanmaktadır: serum albumin ve beta 2-mikroglobulin (B2M). Serum B2M düzeyi böbrek yetmezliği olan hastalarda artmaktadır. Bu, yüksek B2M seviyesinin böbrek yetmezliği olan MM hastalarında her zaman tümör yüküyle ilişkili olmadığı anlamına gelir. Bu nedenle, bu hastalar gerçekte olduğundan daha üst ISS evresine sahip olabilir. Bu çalışmada, böbrek yetmezliği olan MM hastalarında ISS'nin sağkalımı öngörmedeki başarısını değerlendirmeyi amaçladık.

Yöntemler: Merkezimizde otolog kök hücre nakli (OKHN) yapılan 172 MM hastanın verileri retrospektif olarak incelendi. Hastalar Ulusal Böbrek Vakfı Renal Hastalık Kalite Sınıflamasına göre 5 böbrek fonksiyon evresine ayrıldı.

Bulgular: OKHN sonrası genel sağkalım (OS), ISS1 hastalarında 21 ay, ISS2 hastalarında 20 ay ve ISS3 hastalarında 18 ay olarak bulundu. Böbrek fonksiyonuna göre evre 0-1 olan hastalarda OS 18 aydı, evre 2-3-4-5 hastalarda 30 aydı. Tüm ISS evrelerinde, böbrek yetmezliği olan hastalar ile normal böbrek fonksiyonları olan hastalar arasında OS açısından istatistiksel olarak anlamlı fark bulunmadı.

Sonuç: Verilerimiz, ISS'nin genel sağkalımı öngörmedeki öneminin böbrek yetmezliğinden bağımsız olduğunu ortaya koymaktadır.

Anahtar kelimeler: Multipl myelom, renal yetmezlik, uluslararası evreleme sistemi

INTRODUCTION

Multiple myeloma (MM) is a plasma cell disorder in which clonal cells produce a monoclonal immunoglobulin[1]. It is the second most prevalent hematological malignancy. The median age at diagnosis is 70 years and two-thirds of the patients are older than 65 years[2]. Significant improvements have been observed in prognosis with the addition of a number of novel agents to the treatment options in recent years[3]. Prognosis of patients with MM is heterogeneous. The structure of bone marrow micro-environment, age and comorbidities of patients were shown to be significant prognostic factors[4].

Today, International Staging System (ISS) is the most commonly used staging system for patients with MM 4. ISS has been verified in patients treated with autologous stem cell transplantation (ASCT) or conventional chemotherapy or novel agents[3]. ISS is based on 2 variables: serum levels of albumin and beta 2-microglobulin (B2M)[4]. B2M generally increases in lymphoid malignancies and it has a strong correlation with tumor burden. However, serum B2M level also increases in patients with renal failure. This means that the elevated serum level of B2M is not always correlated with tumor burden in MM patients who have renal failure. Therefore, these patients may have further ISS stages than they really have. At the time of diagnosis, 20 to 30% of MM patients have renal failure [5-9]. So up to 30% of the MM patients may have further ISS stages than they really have. It is neccessary to verify the prognostic value of ISS in patients with MM who have renal failure. Therefore, in this study, we aim to study the success of ISS in predicting survival in MM patients with renal failure.

METHODS

The data of 172 MM patients who were performed ASCT in our center between 2010 and 2018 were retrospectively analyzed. *Ethical approval* for this study was *obtained from* the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital(12/2019). The tandem transplant patients described as the patients that underwent second ASCT within 6 months after the first ASCT without progression or relapse were not included in the study. The patients whose glomerular filtration rates (GFR)

at the time of diagnosis were missing in the database or the patients who were referred from other hospitals were excluded from the study. ISS was used for risk classification[4].

GFR was calculated with the formula of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPC) which uses the variables of plasma creatinine, age, gender and race. The following staging was implemented according to the National Kidney Foundation-Kidney Diseases Quality Classification: patients with GFR>120 ml/min stage 0, patients with GFR 90-119 ml/min stage 1, patients with GFR 60-89 ml/min stage 2, patients with GFR 30-59 ml/min stage 3, patients with GFR 15-29 ml/min stage 4, patients with GFR under 15 ml/min or dependent on dialysis stage 5[10]. Patients were grouped as: the patients with mild to severe renal failure (Stage 2-3-4-5) and normal renal function (Stage 0-1).

As conditioning regimen 140 mg/m^2 melphalan was used in patients at the age of ≥70 years or with a serum creatinine level of ≥2 mg/ml whereas the others received 200 mg/m2 melphalan as conditioning regimen. The treatment response was evaluated according to International Multiple Myeloma Workgroup (IMWG) criteria[11]. Overall survival (OS) was defined as the duration from the date of transplant to the date of death.

The statistical analyses were performed with SPSS V21.0 (SPSS Inc., Chicago, IL) software. Descriptive statistics were used to summarize the data. Categorical data were reported as rates; numerical data were reported as median and average ±standard deviation. Kruskal Wallis test was used for the comparisons among the groups. Kaplan Meier test was used for PFS and OS, and log-rank tests were used for the impacting factors.

RESULTS

The characteristics of the patients are given in Table I. 61 patients were in ISS-1; 58 patients were in ISS-2; 53 patients were in ISS-3 groups.

Table I: Patients characteristics

	General Patient Population (n) = 172
Age (median)	56 years (29-81)
Gender	Female (n):75/ Male (n):97
MM Group	Heavy chain (n):127 Light chain(n):40 Non-secretory (n): 4 Not evaluated (n):1
ISS	ISS I(n): 61 ISS II(n): 58 ISS III(n): 53
R-ISS	R-ISS I(n): 31 R-ISS II(n): 74 R-ISS III(n): 11 Not evaluated (n): 56
Durie Salmon stage	DS1(n): 10 DS2(n): 14 DS3(n): 136 Not evaluated (n): 12
Pre-transplantation response	CR(n): 64 VGPR(n):39 PR(n):49 Stabil(n):15 Refractory(n):4 Not evaluated(n): 1
Renal Failure Stages (CKD-EPC)	Stage 0(n):14(8.1%) Stage 1(n):106(61.6%) Stage 2(n):39(22.7%) Stage 3(n):12(7%) Stage 4(n):1(0.6%) Stage 5(n):0
Number of therapy lines received	1 line(n): 44 2 lines(n): 101 3 lines(n):21 4 lines(n): 3 5 lines(n):1 Not evaluated (n):2
Conditioning Regimen	140mg/m^2(n):19 200mg/m^2 (n): 153
Radiotherapy	Received(n): 28 Not received (n):144
The quantity of infused CD34$^+$ cells (median)	4.6 *10^6/kg

MM: Multiple Myeloma; ISS: International Staging System; R-ISS: Revised International Staging System

When the patients were divided into 2 groups as normal renal function (stage 0-1) and renal failure (stage 2-3-4-5) groups according to the Kidney Disease Quality Classification of the National Kidney Foundation, the rate of renal failure in ISS1, ISS2 and ISS3 patients were 21%, 20.7% and 50.9% respectively. The rate of renal failure in ISS3 patients were higher than those of the patients in ISS1 and ISS2 stages at a statistically significant level (p:<0.001). While the rate of renal failure in patients at the age of ≥65 years was 56.5%, it was found 27.5% in patients under the age of 65 (p:<0.001). OS of ISS1, ISS2 and ISS3 patients were 21 months, 20 months and 18 months respectively (p:0.231) (Table II).

Table II: The relationship between ISS stages and overall survival

MM Stage	OS (Overall Survival) months (%95 CI)	p value
ISS 1	21 (8,16-33,83)	0.231
ISS 2	20 (13,76-26,23)	
ISS 3	18 (4,69-8,80)	

ISS, International Staging System

OS according to renal failure stages were found as follows: 8 months in stage 0, 19 months in stage 1, 42 months in stage 2, 25 months in stage 3, and 23 months in stage 4 (p: 0.95) (Table III).

Table III: The relationship between renal failure and overall survival

Stages of renal failure	OS (Overall Survival) months (%95 CI)	p value
Stage 0	8 (0-18,73)	0.950
Stage 1	19 (15,62-22,37)	
Stage 2	42 (13,94-70,05)	
Stage 3	25 (0-50,48)	
Stage 4	23	
Stage 0-1	18 (14,37-21,62)	0.606
Stage 2-3-4-5	30 (18,24-41,76)	

ISS, International Staging System

OS in stage 0-1 patients was 18 months, it was 30 months in stage 2-3-4-5 patients. When the OS in stage 0-1 compared to OS in stage 2-3-4-5, there was no statistically significant difference regarding OS (p: 0.606). OS according to ISS and renal failure stages were given in Table 4. There was no statistically significant difference regarding OS between patients with renal failure and normal renal function in all ISS stages (Table IV).

Table IV: The relationship between renal failure, ISS and OS

MM Stage	Renal Failure Stage	OS (Overall Survival) months (%95 CI)	p value
ISS 1	Stage 0-1	20 (13,21-26,79)	0.433
	Stage 2-3-4-5	42 (-)	
ISS 2	Stage 0-1	19 (15,21-22,78)	0.700
	Stage 2-3-4-5	47 (21,39-72,60)	
ISS 3	Stage 0-1	16 (6,28-25,71)	0.384
	Stage 2-3-4-5	23 (7,89-38,10)	

ISS, International Staging System; MM, Multiple Myeloma

DISCUSSION

It has been considered that the patients with renal failure would be included in higher ISS stages due to increased B2M associated not with the tumor burden of myeloma but renal failure; therefore, they could possibly have different clinical expectations as compared to the patients at the same ISS stage without renal failure. Approximately 30% of MM patients have renal failure of some extent at the time of diagnosis[5-9], and most of these patients are classified as ISS-3 due to increased levels of B2M; therefore, it is important to verify the survival predictive value of ISS in MM patients with renal failure.

In a previous study, in ISS-3 patients, they found out that renal failure, which was evaluated by GFR or serum creatinine levels, did not have any impacts over OS in univariate and multivariate analyses[12]. In our study, although the patients

with renal failure in all ISS stages had longer OS compared to the patients without renal failure, this did not create a statistically significant difference. This situation supports that the prognostic significance of ISS is independent from renal failure.

In a study, although renal failure was more prevalently observed in MM patients at the age of ≥65 than the MM patients under the age of 65 years, renal failure was found as an independent prognostic factor only in the patients at the age of ≥65 years[12]. Similarly, we found a statistically significant difference between the patients at the age of ≥65 years and the patients under the age of 65 years regarding the rate of renal failure ($p<0.001$). The frequency of renal failure in the MM patients at the age of ≥65 years was higher than those of the patients under the age of 65 years. Moreover, the cause of renal failure could be associated with accompanying comorbidities other than MM in myeloma patients. MM is an older age disease so the rate of accompanying chronic disease rate is also high. In a multicenter study including 3894 MM patients, it was shown that B2M significantly increased with age which may be related to renal failure whereas albumin decreased with age. In combination with the B2M increase there was an increase in the proportion of patients with higher ISS stages in the older groups but they showed that ISS remained its survival predictivity in all age groups[13].

In a previous study, higher rate of renal failure was found in MM patients with high tumor burden when compared to the MM patients with lower tumor burden[14]. This also indicates that although increased B2M was associated with renal failure in ISS-3 patients with renal failure, it still continues to be a strong indicator of tumor burden. In our study, the rate of patients with renal failure in ISS3 was higher than those of the patients in ISS2 and ISS1 stages at a statistically significant level as well ($p<0.001$).

Furthermore, B2M is related with tumor burden, tumor-micro-environment interactions and various factors associated with patients (such as renal function and immune deficiency)[4,15,16]. In spite of ISS's significant prognostic value, we have to consider the fact that ISS only defines three prognostic groups. However, myeloma patients are characterized by significant heterogeneity which would not fit only three prognostic categories.

In conclusion, ISS was not developed for individual treatment decisions, but it is a beneficial tool for classification and comparisons in clinical trials, and it provides significant prognostic information for MM patients. Our data reveals that the significance of ISS to predict overall survival is independent from renal failure.

Ethics Committee Approval: Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (12/2019).

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