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Follow-up of patients given isoniazid prophylaxis in multiple myeloma patients underwent autologous stem cell transplantation

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ABSTRACT

Aims: With the developments in recent years, multiple myeloma (MM) a plasma cell discrazy has become a disease whose life expectancy is expressed in 10 years. Stem cell transplantation still maintains its place in this disease and post-transplant prophylaxis is important. One of these is antituberculosis prophylaxis. We wanted to introduce this barren subject.

Methods: A retrospective screening of patients with MM who were started on isoniazid (INH) prophylaxis and underwent autologous stem cell transplantation was planned.

Results: Antituberculosis prophylaxis was given to 25 patients (6.5%) out of 380 MM transplant patients. Purified protein derivative skin test was positive in 20 of the patients who were given INH prophylaxis. Fifteen patients had pulmonary findings compatible with latent tuberculosis infection. Ten patients had both. No patients progressed to active tuberculosis. There was no difference between those who used INH/not in terms of obtaining complete remission or very good partial complete remission and other responses (p=0.220). And there was no survival difference between INH users and others.

Conclusion: Follow-up of patients receiving INH prophylaxis is also important. Histopathological findings obtained with autopsy of myeloma patients who died with pneumonia after autologous transplantation with INH prophylaxis will answer the question of whether it was tuberculosis.

Keywords: Myeloma, transplantation, INH prophylaxis

INTRODUCTION

Multiple myeloma (MM) is a malignant hematological monoclonal plasma cell disease. Autologous stem cell transplantation (ASCT) after high-dose chemotherapy still maintains its place in consolidation despite new drug options in MM patients.

In the 20 years preceding the last 5 years, the 5-year life expectancy of MM patients has increased approximately 2 times (from 27.2% to 50.2%).[1]

In myeloma patients with a higher incidence of tuberculosis than in the normal population,[2] an increased risk can be expected after ASCT.

The chest diseases department is one of the key units that is consulted for pre-transplant eligibility assessment of patients undergoing ASCT. As a result of this consultation, it is recommended that patients who have a positive image on thorax CT and/or PPD test that may be compatible with past pulmonary tuberculosis disease should undergo transplantation with anti-tuberculosis prophylaxis. The most recommended prophylactic drug is isonicotinic acid hydrazide (INH).

In this study, we aim to determine how many myeloma patients who underwent ASCT received prophylaxis and whether there were any problems in their follow-up.

METHODS

The study was carried out with the permission of Ethics Committe of Kayseri Erciyes Universtiy (Date: 22.09.2021, Decision No: 2021-622). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Gathering data from 491 Multiple Myeloma ASCTs that were received from patients who underwent hematopoietic stem cell transplantation at Kayseri Erciyes University between December 2008 and December 2019, a total of 380 patients, 240 men, and 140 women, were evaluated retrospectively. File records of how many of these patients we gave antituberculosis prophylaxis treatment were scanned and recorded.

Internationally established criteria were used to determine the risk of reactivation for tuberculosis. According to the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC), 5 mm and above are considered positive in immunocompromised individuals. Immunocompromised individuals: HIV positivity, acquired immunodeficiency syndrome, chronic renal failure on dialysis, individuals who have taken high-dose corticosteroids for a long time [Steroid doses equivalent to 15 mg and above prednisone dose per day for 2-4 weeks are considered high enough dose], those who have undergone organ or haematological transplantation and other conditions where immunosuppressive therapy is given are those with reticuloendothelial system malignancies.[3]

Statistical Analysis

The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk test, histogram, and q-q graphs. Two-sample independent t-test was used in the analysis of quantitative data. Fisher-Freeman-Halton exact and Pearson chi-square tests were used to compare categorical data. Mean, standard deviation statistics, frequency, and percentage statistics were used to summarize the data. Significant risk factors on survival were examined with Cox regression analysis, and significant variables were determined by the forward selection method (Forward LR). The hazard ratios obtained from the model were evaluated with a 95% confidence interval. Analysis of the data was performed in TURCOSA (Turcosa analytics Ltd Co, Turkiye, (www.turcosa.com.tr) statistical software. The statistical significance level was accepted as $p<0.05$.

RESULTS

It was determined that a total of 25 patients used INH prophylaxis. Of these patients, 19 were male and 6 were female ($p>0.05$).

In addition, there was no difference between those who received INH and those who did not, in terms of gender, age at the time of transplantation, comorbidity, the last pre-transplant chemotherapy regimen, transplantation conditioning melphalan dose, transplantation response, and follow-up time. As the last chemotherapy regimen before transplantation, the majority of patients in both groups used a regimen containing bortezomib drug. The rate of two or more comorbid diseases was approximately 10% percent and was similar in both groups.

Baseline International Staging System (ISS) stage and pre-transplant remission status differed between groups. Approximately 50% of those who did not use INH had the initial disease stage of ISS at stage 3, while the majority of those who received INH had stage 2 diseases ($p=0.053$, Fischer 0.039). Those who did not use INH had higher remission rates at the time of transplantation, and this difference was statistically significant ($P=0.047$)

Pretransplant baseline characteristics are shown below in Table 1. PPD was positive in 20 of the patients who were given INH prophylaxis. 15 patients had pulmonary findings. Ten patients had both PPD positivity and pulmonary findings. The acid resistance in mycobacterium tuberculosis test was suspicious in the bronchoalveolar lavage sample obtained in one patient.

Table 1. Evaluation of intergroup characteristics before transplantation

Parameters compared	INH use		p
	No	Yes	
Age	63.50±9.10	63.16±8.03	0.855
Gender			
Male	221 (62.3)	19 (76.0)	0.168
Female	134 (37.7)	6 (24.0)	
Stage			
Stage1	63 (21.6%)	6 (28,6%)	0.053
Stage2	69 (23.6%)	9 (42.9%)	Fischer 0.039
Stage3	160 (54.8%)	6 (28.6%)	
Comorbidities			
Less than 2 chronic diseases	321 (90.4%)	22 (88%)	0.702
>2 or more chronic diseases	34 (9.6%)	3 (12.0%)	
Last chemotherapy regimen pretransplant			
VAD	67(18.9%)	3 (12.0%)	0.187
BOR	233 (65.8%)	21 (84.0%)	
LEN	40 (11.3%)	0 (0.0%)	
Pretransplant-Condition			
CR or VGPR	262 (82.9%)	16 (66.7%)	0.047
Other(PR and less)	54 (17.1%)	8 (33.3%)	
Melphalan dose			
200 mg/m^2	299 (84.2%)	23 (92.0%)	0.296
140 mg/m^2	56 (15.8%)	2 (8.0%)	

INH: Isonicotinic acid hydrazide, VAD: Vincristine-doxorubicin-dexamethasone, BOR: Bortezomib, LEN: Lenalidomid, CR: Complete remission, VGPR: Very good partial complete remission, PR: Partial remission

Quadruple antituberculosis (INH+Rifampicin+etambutol+pirazinamid) treatment was started in one patient out of 25 patients, Rifampicin + INH was started in another patient, and only INH prophylaxis was started in all the remaining patients. In the follow-ups, liver function test disorder was evaluated as INH-related in 5 patients and it was interrupted. None of the patients progressed to active tuberculosis. A summary of patients at risk of tuberculosis reactivation is shown in Table 2.

Table 2. Patients at risk of tuberculosis reactivation

TST with PPD	Radiographic chest signs		
	Positive	Negative	Total
PPD positive	10	10	20
PPD negative	5	355	360
Total	15	365	380

TST: tuberculin skin test, PPD: purified protein derivative

There was no difference in terms of using INH with or without renal function test disorder. While 24% of INH users were hepatic serologic test positive, 12.1% of those who did not use INH were positive ($p=0.087$). CMV PCR positivity was 20% (5pts) in INH users and 6.2% (22pts) in non-users ($p=0.024$).

After transplantation, there was no difference between those who used INH and those who could not, in terms of obtaining CR or VGPR and rates of other responses ($p=0.220$). However,

when evaluated in detail, the CR rate is 40.8% in those who do not use INH, while it is 20% in those who do; while the rate of VGPR was 36.8% in non-users, it was 45% in users. Stable disease was found in 7.1% of those who did not use INH and 25% of those who used it (p=0.031).

Initially, despite the apparent favor towards non-users of INH in terms of life expectancy, there was no discernible disparity in overall survival between individuals who utilized INH and those who did not. (Figure).

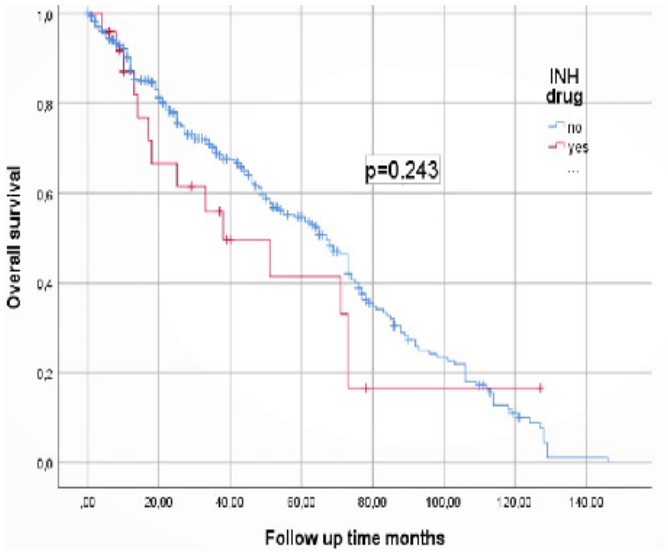

Figure . Overall Survival (months) graphic of INH users or not by Kaplan-Meier plot

DISCUSSION

New drugs for myeloma attract a lot of attention, but prophylaxis remains in the shadows. In the prophylactic and antimicrobial treatment consensus reports regarding high-dose chemotherapy and autologous stem cell transplantation, although CMV, herpes, and hepatitis b prophylaxis are included in the guidelines, antituberculosis prophylaxis is not mentioned.[4] According to a recently published review about consensus and recommendations for myeloma patient infection prevention, bacterial viral and fungal infections have taken a large place.[5] Tuberculosis is mentioned in only one sentence, perhaps because it is thought to be infrequent. However, tuberculosis disease is more common in MM patients compared to the normal population. In the study in which the tuberculosis risk in MM was compared with the healthy cohort; age 65 and over, alcohol use, and daily use of prednisone 5 mg or more were found to be factors associated with increased risk.

Eighty-three (2.1%) of 3979 MM patients were tuberculosis-positive, more than the normal population (1.5%). In addition, the mortality of these positive MM patients was found to be higher than negative myeloma patients.[2]

In our study, there was no difference in terms of age at the time of transplantation of patients who were not given INH prophylaxis. In our patients, the rate of patients with PPD-positive or pulmonary findings who were started prophylaxis was 6.5% (25/380). While the rates of patients diagnosed with tuberculosis were mentioned in the above publication, patients at risk of tuberculosis reactivation were discussed in our article. No patient progressed to active tuberculosis. Besides, there was no difference in the survival of patients who received or did not receive INH.

Gitman et al.[6] reported that they investigated the tuberculosis risk in 170 myeloma patients; 26 patients were found to be at high risk for reactivation and prophylactic treatment was started whereas 14 of them had positive tuberculin skin test. The novelty of the current article is due to a retrospective review of patients who started prophylaxis due to the risk of tuberculosis reactivation in myeloma transplant patients, and it is a survey conducted with more patients. As stated in this study and the study of Gitman et al., a substantial number of patients receive INH prophylaxis, and the use of this drug, which also has side effects and drug interactions, in haematology is a task that requires special attention.

There are conflicting publications about the effect of drugs used in the treatment of myeloma on tuberculosis. Thalidomide is found effective in drug-resistant tuberculosis, however, a case is reported after new generation immunomodulatory drug lenalidomide maintenance in MM patients.[7,8] None of the patients who were given antituberculosis prophylaxis had a previous history of lenalidomide use.

Since INH is a molecule that interacts with other drugs, the duration of use after transplantation is also an issue that should be noted. In our study, 5 patients out of 25 patients using INH had liver function test disorders, so INH was interrupted and hepatic serological tests were also performed. It was started again when the liver function test improved in the follow-ups. Although 24% of patients using INH were hepatic serology positive, these patients were not the same patients who developed liver function test abnormalities and had to interrupt INH.

Another significant finding of the present study is that there is a positive relationship between INH use and CMV positivity, which is raw data that needs to be supported by larger studies. Since it may take up to 6 months for the immune system to fully recover after autologous transplantation, it will be a period open to opportunistic infections.

CONCLUSION

Some of our autologous stem cell transplant patients with myeloma who receive INH prophylaxis die from pneumonia. Determining whether there is tuberculosis activation or not by post-mortem studies will shed light on this area. In countries where tuberculosis is endemic, tuberculosis should be kept in mind in the differential diagnosis in case of unexplained infection in hematological malignant patients with or without post-transplant fever.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ethical Committe of the Medicine Kayseri Erciyes Universtiy (Date: 22.09.2021, Decision No: 2021-622).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
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Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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