WBC Count and WBC to Hb Ratio Could Predict Short-Term Recurrence Rate in Multiple Myeloma Patients Underwent Autologous Stem Cell Transplantation

Hengameh Mojdeganlou[1], Ata Abbasi[1,2], Rahim Asghari[2]

[1] *Department of Pathology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran*

[2] *Hematology, Immune Cell Therapy and Stem Cells Transplantation Research Center, Clinical Research Institute, Urmia University of Medical Sciences, Urmia, Iran*

Received: 03 Jan. 2022; Accepted: 01 Feb. 2023

Abstract- Multiple myeloma (MM) is a hematologic malignancy with a variable clinical course. We investigated the prognostic role of routine laboratory factors including CBC indices and serum vitamin D levels to predict MM recurrence after receiving an autologous stem cell transplant (ASCT). 29 patients were enrolled. Before ASCT, demographic data and CBC, serum Cr, and Vit D levels were obtained. Patients underwent bone marrow aspiration (BMA) and biopsy (BMB) before ASCT and pretransplant plasma cell counts were also evaluated. Patients were followed for 6 months and BMA and biopsy were done in the 3rd and 6th month of the follow-up to detect recurrence. Overall, 9 patients were reported to have recurrence. The patient's WBC count mean was 13.3±11.6. WBC count was lower in patients with overall recurrence (*P*=0.005). Patients were divided into 2 groups according to WBC count (<5.5 10^9/L and ≥5.5 10^9/L) and we found that WBC count <5.5 10^9/L was associated with increased risk of recurrence by 15.2 times (Odds ratio: 15.2, 95%CI: 1.4-168, *P*=0.005). We also evaluated Wbc to Hb ratio (Wbc/Hb) and found that Wbc/Hb <1 had a significant statistical relationship with overall recurrence (*P*=0.026) as patients with WBC/Hb <1 were in 9.8 times increased risk of recurrence (Odds ratio:9.8, 95% CI: 2-93.5, *P*=0.026). pretransplant WBC <5.5 10^9/L and WBC/Hb <1 were associated with 9.8 and 15.2 times increased risk of myeloma recurrence and could be useful predictive factors for a patient's short-term recurrence.

Acta Med Iran 2023;61(4):211-215.

Keywords: Multiple myeloma; Complete blood count; Recurrence; Prognosis

Introduction

Multiple myeloma (MM) is a hematologic malignancy derived from B cells and it accounts for about 1% of all cancers (1). It is presented with high ESR, anemia, lytic bone lesions, renal failure, and hypercalcemia, due to end-organ damage (2). Multiple myeloma occurs in all races, but it is higher in blacks (1).

Although the incidence of the disease has increased during past decades, the mortality has reduced and the outcome and survival of patients with multiple myeloma (MM) have improved (1,3,4). The increased incidence of the disease is probably not an actual incidence increase but probably is associated with the improved diagnostic techniques which have helped to find patients in earlier stages (1).

Multiple myeloma is a very heterogeneous disease with a highly variable clinical course and outcome (5). This diversity derives from many host and disease factors (5,6).

Many factors such as age, gender, blood urea level, hemoglobin (Hb), serum creatinine level and extent of bone marrow involvement by myeloma cells have shown influence on the prognosis of multiple myeloma (5-8). Understanding these factors would help us to better evaluate disease outcome and survival duration which could be followed by personalized and optimized therapy. Patients' survival has been significantly improved following the utilization of novel agents and

Corresponding Author: A. Abbasi
Department of Pathology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
Tel: +98 9124397395, E-mail address: aabbasi@alumnus.tums.ac.ir

autologous stem cell transplantation (ASCT) (3,9).

Two types of stem cell transplantation exist: autologous and allogeneic. Autologous stem cell transplantation was introduced in the 1990s as first-line therapy for patients under 65 years of age (10).

Allogeneic transplantation was developed earlier than ASCT but it has limitations because of its high toxicity (such as infections & graft versus host disease) (11).

Studies have shown that ASCT can be safely performed in multiple myeloma patients and bring them into remission and is associated with improved response rate and survival (12,13). Previously a combination of high-dose therapy with melphalan followed by autologous stem cell transplant (HDT/ASCT) has been the standard regimen for MM Patients. Following modern therapy with immunomodulatory drugs and proteasome inhibitors, patients are achieving improved outcomes (14).

Since ASCT is a novel and also expensive method of treatment in patients with MM it would be very important to explore and define the factors which can influence transplantation outcome. So, In this study, we investigated the prognostic role of some host & laboratory factors such as age, gender, white blood cell count (WBC), Hb, hematocrit, platelet count, vitamin D level and pretreatment extent of bone marrow involvement to predict MM patient's survival (after 6 months follow up) after receiving bone marrow transplantation.

Materials and Methods

About 300 patients with multiple myeloma were initially screened at Imam Khomeini Hospital, Urmia, Iran, during 2017-2020. Thirty patients were enrolled in this study, who underwent autologous stem cell transplant (ASCT) during this period. All 30 patients received the same regimen before the transplant (Melphalan followed by lenalidomide) and followed for 6 months. Patients underwent bone marrow aspiration (BMA) and biopsy (BMB) before the ASCT and after the transplant at intervals of three and six months. We excluded 1 patient who did not attend on the 3rd and 6th month for bone marrow biopsy evaluation.

The study was approved by the Human Research Ethics Committee of Urmia University of medical sciences (IR.UMSU.REC.1399.008)

Plasma cell count

The prepared glass slides were assessed and the plasma cell count was determined by estimation of the percentage of plasma cells in BMA and on immunohistochemistry (CD 138) stained BMB slides microscopically. A plasma cell percentage<5% is considered normal.

Patient demographics such as age and gender, date of ASCT and pretransplant laboratory data including WBC, Hb, Hct, plt, creatinine (Cr) and Vitamin D (Vit D) were also collected from hospital medical records. Vitamin D (Vit D) Levels <30 ng/ml were considered deficient & levels ≥30 ng/ml were considered normal.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The normality of data was evaluated with the Kolmogorov-Smirnov test. Numeric data were reported as mean±SD (standard deviation) and nonparametric data were reported as mean±SEM (standard error of the mean). Chi-squared analyses were performed to assess for statistically significant relationships between variables and proportions. Numerical data were evaluated using the student T-test. $P<0.05$ was considered significant.

Results

Twenty-nine patients were included in the final analysis. Patient's mean age was 55.86±18 (38 to 73).

Seventeen (58.6%) were men and 12 (41.4%) were women. Patients' demographic data are mentioned in Table 1. All patients underwent bone marrow aspiration and biopsy before ASCT, and 3 and 6 months after ASCT.

Overall, 9 (30%) patients were reported to have a recurrence, of these 9 patients, 3 were in the 3rd month and 6 Were in the 6th month after ASCT (6 were men and 3 were women).

The mean of patients' WBC count was 13.3±11.6 (range from 2.08 to 56.2 10^9/L, median=8.4 10^9/L, mode=5.8 10^9/L). White blood cell count was lower in patients with overall recurrence (recurrence in the 3rd or 6th month) (*P*:0.005). Patients were divided into 2 groups according to WBC count (<5.5 10^9/L and ≥5.5 10^9/L) and we found that WBC count <5.5 10^9/L was associated with increased risk of recurrence by 15.2 times (Odds ratio: 15.2, 95%CI: 1.4-168, *P*=0.005). We also evaluated Wbc to Hb ratio (Wbc/Hb) and found that Wbc/Hb< 1 had a significant statistical relationship with overall recurrence (*P*=0.026) as patients with WBC/Hb< 1 were in 9.8 times increased risk of recurrence (Odds ratio:9.8, 95% CI: 2-93.5, *P*=0.026), (Table 2). The

receiver operating curve (ROC) was obtained and the area under the curve (AUC) for WBC count <5.5 10^9/L and WBC/Hb< 1 were 0.836 and 0.794, respectively (Figure 1). Patients' age, Hct, plt and Cr did not significantly influence malignancy recurrence.

Table 1. Patient's demographic data

Gender (N)	**Male: 17, female: 12**
Age (mean ± SD*)	55.8 ± 9
Pretransplant plasma cell percentage (mean±SEM)**	4.7 ± 1.6
Post-transplant plasma cell percentage (3rd month) (mean±SEM)	2.8 ± 0.3
Post-transplant plasma cell percentage (6th month) (mean±SEM)	7.9 ± 3.2
Vitamin D (mean±SEM)	31 ± 5.3
WBC (mean±SD)	14 ± 11
Hb (mean±SD)	11.9 ± 1.4
Plt (mean±SD)	180 ± 70
Creatinine (mean±SD)	1.3 ± 0.4

*SD: Standard Deviation
**SEM: Standard Error Of Mean

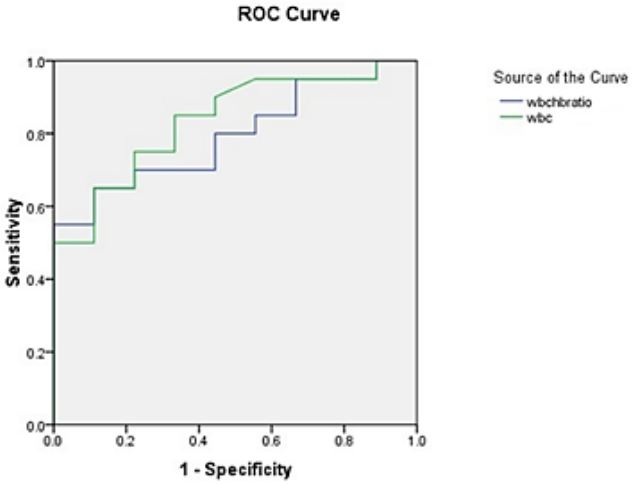

Figure 1. Showing ROC curve analysis (receiver operating curve) for WBC count and WBC to hemoglobin ratio (WBC/Hb) and myeloma recurrence. The area under the curve (AUC) were 0.836 and 0.794, respectively

Table 2. Relationship between WBC, WBC/Hb and myeloma recurrence

		Recurrence	Non-recurrence	*P*
WBC	**<5.5 (10^9/L)**	4	1	0.009*
	>5.5 (10^9/L)	5	19	
WBC/Hb	**>1**	1	11	0.026*
	<1	8	9	

**P*<0.05 is statistically significant.

Discussion

Multiple myeloma is a heterogeneous disease and patients survival is variable (8). Prognostic factors such as hemoglobin, Cr, platelet count albumin, etc. were shown to be associated with the outcome. Many Studies have been performed to assess these relationships (8,15,16,17). Our study confirmed the validity of some of these factors in predicting the response rate & recurrence of this disease.

In our analysis, we found a lower recurrence rate in patients with higher WBCs. WBCs< 5.5 10^9/L had a

significant relationship with higher recurrence after 6 months as pretransplant WBC counts below 5.5 10^9/L could increase the risk of recurrence by 15.2 times. We also evaluated the relationship between WBC (10^9/L)/Hb (mg/dl) and overall recurrence (recurrence after 6 months) and Interestingly found that WBC/Hb< 1 increased the risk of recurrence by 9.8 times. According to the literature, our results are unique and there were no other studies to introduce a cutoff value to predict short-term recurrence of the disease before transplantation.

A recent study by Al Saleh AS *et al*., examined the ability of hematopoietic indices to predict outcomes and concluded that variables from a CBC were able to predict overall survival in newly diagnosed MM patients (16).

Similarly, Liu *et al.*, also evaluated the prognostic significance of inflammatory factors including red blood cell distribution width (RDW), neutrophil to lymphocyte ratio (NLR), and platelet count (Plt) in overall survival of MM patients & showed that NLR, RDW and plt could predict the prognosis of these patients (15).

Yang *et al*., discussed the prognostic significance of peripheral Absolute Lymphocyte and monocyte counts (ALC and AMC, respectively) in multiple myeloma patients, who underwent bortezomib therapy. Yang showed that ALC had a significant relationship with overall survival (18).

We did not detect any relationship between patients' age, platelet count, Hb, Hct and Cr with overall recurrence. Contrary to our results Al Saleh AS *et al*., found that older age, thrombocytopenia, macrocytosis and increased serum Cr were predictive of worse outcomes (16).

In recent years many studies have been performed to explore the importance of various predictive factors including b2- microglobulin, albumin, CBC variables & also cytogenetic abnormalities in the survival of patients with multiple myeloma (8,16,17,19).

Along with studies that have focused on the CBC markers, some studies evaluated the utilization of molecular techniques, such as fluorescent in-situ hybridization (FISH) to predict the outcome of multiple myeloma patients (20).

Pawlyn and Davies showed that some molecular variations affect the outcome and overall survival in patients with multiple myeloma. These include Del(17p), Gain(1q), Del(1p), the mutation in CCND1, and DNA repair pathway genes (TP53, ATM, ATR, and ZFHX4), that are associated with adverse outcomes (20).

It is important to note that although many technologies such as FISH, mass spectrometry and next-generation flow cytometry will allow us to better evaluate the patients' outcomes, limitations exist with these technologies, such as high-cost and limited availability as well as limited available data. So it would be of great value to find affordable, feasible and time-saving markers to evaluate patients' outcomes after ASCT.

There are some limitations to our research. Our study population was small. Since the ASCT is a relatively new therapeutic method for MM patients and it has been 3 years that bone marrow transplantation is being performed in our center, a relatively small population was available.

In this study, we have performed a short-term follow-up (6 months) and as a short-term follow-up study, we obtained important cost-effective and very available prognostic factors for clinicians to predict the short-term outcome of the patients. Although long-term follow-up was not our scope, it could give us a better view of prognostic factors & patient survival.

However, this was a practical study, that evaluated the cost-effective prognostic factors such as WBC count and WBC/Hb. We also introduced a useful cutoff value that could help clinicians to predict patients' recurrence at the time of transplantation. As they are affordable and low-priced laboratory markers, the findings of our study could provide applicable short-term predictive factors for MM recurrence in patients who underwent ASCT. Evaluating long-term survival remains a goal of future research.

Along with the usage of novel agents and ASCT, understanding the factors that affect patients' survival and their association with the disease outcome could be a great progress in intervening in the treatment of multiple myeloma patients, who may benefit from this approach. One of the most cost-effective and economical prognostic markers is CBC indices. Our results showed that pretransplant WBC count and WBC/Hb, are available & inexpensive markers that can predict patients' clinical outcomes and overall survival. We introduced two cutoff values for WBC (WBC< 5.5 10^9/L) and WBC/Hb (WBC/Hb< 1) to predict patients' recurrence at the time of transplantation and these two cutoff values could be utilized as a useful predictive factor for patients short term recurrence.

Acknowledgments

This research has been supported by Urmia University of Medical Sciences research grants.

References

1. Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33.
2. Mateos MV, San Miguel JF. Management of multiple myeloma in the newly diagnosed patient. Hematology Am Soc Hematol Educ Program 2017;2017:498-507.
3. Joseph NS, Gentili S, Kaufman JL, Lonial S, Nooka AK. High-risk Multiple Myeloma: Definition and Management. Clin Lymphoma Myeloma Leuk 2017;17S:S80-7.
4. Kumar L, Ramavath D, Kataria B, Tiwari A, Raj A, Chellapuram SK, et al. High-dose chemotherapy followed by autologous stem cell transplant for multiple myeloma: Predictors of long-term outcome. Indian J Med Res 2019;149:730-9.
5. Szudy-Szczyrek A, Szczyrek M, Soroka-Wojtaszko M, Hus M. New prognostic biomarkers in multiple myeloma. Postepy Hig Med Dosw (Online) 2016;70:811-9.
6. Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Bladé J, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412-20.
7. Dawson AA, Ogston D. Factors influencing the prognosis in myelomatosis. Postgrad Med J 1971;47:635-8.
8. Bataille R, Durie BG, Grenier J, Sany J. Prognostic factors and staging in multiple myeloma: a reappraisal. J Clin Oncol 1986;4:80-7.
9. Patriarca F. Frontline therapy in multiple myeloma: fast start for a long game. Lancet Haematol 2019;6:e600-1.
10. Tangen JM, Tjønnfjord GE, Gulbrandsen N, Gedde-Dahl T, Stormorken E, Anderson K, et al. Improved outcome in patients following autologous stem cell transplantation for multiple myeloma in south eastern Norway 2001-2010: a retrospective, population based analysis. BMC Cancer 2018;18:801.
11. Munker R, Monohan G. Progress in multiple myeloma. Indian J Med Res 2019;149:693-4.
12. Aggarwal M, Agrawal N, Yadav N, Verma P, Ahmed R, Mehta P, et al. Autologous stem cell transplantation in first remission is associated with better progression-free survival in multiple myeloma. Ann Hematol 2018;97:1869-77.
13. Hari P. Recent advances in understanding multiple myeloma. Hematol Oncol Stem Cell Ther 2017;10:267-71.
14. Dhakal B, Szabo A, Chhabra S, Hamadani M, D'Souza A, Usmani SZ, et al. Autologous Transplantation for Newly Diagnosed Multiple Myeloma in the Era of Novel Agent Induction: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4:343-50.
15. Liu S, Shi J, Guo H, Xu F, Wei M, Sun K, et al. Prognostic Significance Of The Inflammatory Index-Based Scoring System In Patients Preliminarily Diagnosed With Multiple Myeloma In The Bortezomib-Based Chemotherapy Era. Cancer Manag Res 2019;11:9409-20.
16. Al Saleh AS, Sidiqi MH, Dispenzieri A, Kapoor P, Muchtar E, Buadi FK, et al. Hematopoietic score predicts outcomes in newly diagnosed multiple myeloma patients. Am J Hematol 2020;95:4-9.
17. Ng AC, Kumar SK, Rajkumar SV, Drake MT. Impact of vitamin D deficiency on the clinical presentation and prognosis of patients with newly diagnosed multiple myeloma. Am J Hematol 2009 ;84:397-400.
18. Yang Y, Liu Z, Wang H. Peripheral Absolute Lymphocyte Count: An Economical and Clinical Available Immune-Related Prognostic Marker for Newly Diagnosed Multiple Myeloma. Med Sci Monit 2020;26:e923716-1-8.
19. Bashir Q, Khan H, Orlowski RZ, Amjad AI, Shah N, Parmar S, et al. Predictors of prolonged survival after allogeneic hematopoietic stem cell transplantation for multiple myeloma. Am J Hematol 2012;87:272-6.
20. Pawlyn C, Davies FE. Toward personalized treatment in multiple myeloma based on molecular characteristics. Blood 2019;133:660-75.