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

Hengameh Mojdehavanlou1, Ata Abbasi1,2, Rahim Asghari2

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

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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: 2.93-3.5, 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.

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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
Lower WBC count and WBC/Hb predicts higher recurrence rate in multiple myeloma patients

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 56.2 10⁹/L, median=8.4 10⁹/L, mode=5.8 10⁹/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 (<5.5 10⁹/L and ≥5.5 10⁹/L) and we found that WBC count <5.5 10⁹/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

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

*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

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Non-recurrence</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC &lt; 5.5 (10^9/L)</td>
<td>4</td>
<td>1</td>
<td>0.009*</td>
</tr>
<tr>
<td>WBC &gt; 5.5 (10^9/L)</td>
<td>5</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>WBC/Hb &gt; 1</td>
<td>11</td>
<td>9</td>
<td>0.026*</td>
</tr>
<tr>
<td>WBC/Hb &lt; 1</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

*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
Lower WBC count and WBC/Hb predicts higher recurrence rate in multiple myeloma patients

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

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References


