http://www.medscidiscovery.com

OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2020; 7(4):470-4

Research Article Doi: 10.36472/msd.v7i4.372

Bone marrow plasma cell ratio, is it must to evaluate before autologous stem cell transplantation in multiple myeloma?

Semih Başcı[1], Tuğçe Nur Yiğenoğlu[1], Mehmet Bakırtaş[1], Bahar Uncu Ulu[1], Derya Şahin[1], Tahir Darçın[1], Jale Yıldız[1], Dicle İskender[1], Nuran Ahu Baysal[1], Mehmet Sinan Dal[1], Merih Kızıl Çakar[1], Fevzi Altuntaş[1]

Abstract

Objective: Complete remission in multiple myeloma (MM) is a defined as having a <5% bone marrow plasma cell (BMPC) ratio plus negative serum and urine immunofixation tests. However, it is necessary to reassess whether or not the bone marrow plasma cell ratio should be determined before transplantation in secretory multiple myeloma patients. A significant decrease in monoclonal protein levels or having negative serum and urine immunofixation tests after induction therapy might be enough to indicate chemo-sensitivity.

Material and Methods: In this study, the data of 177 multiple myeloma patients that underwent autologous stem cell transplantation (ASCT) in our center were retrospectively evaluated.

Results: We found a statistically significant difference in the post-ASCT response rates between the patients with a pre-ASCT BMPC ratio <5% vs BMPC ratio ⩾5% (p:<0.001*). The 2-year progression-free survival (PFS) of the patients with BMPC ratio <5% and ⩾5% post-ASCT was found 24% and 25% (median PFS 11 months (95% CI; 6,68-15,31) vs 12 months (95% CI; 9,47-14,53)) respectively (p: 0.900). The 2-year overall survival (OS), was 67% and 63% (median OS 35 months (95% CI; 25,59-44,41) vs 40 months (95% CI; 27,52-52,47)) respectively (p: 0.341).

Conclusion: Patients with decreasing monoclonal protein in serological tests, the pre-ASCT BMPC ratio was not found to have an impact on neutrophil and platelet engraftment durations, transplantation related mortality (TRM), PFS and OS. Our study suggests that in MM patients with measurable disease, it is not required to evaluate the BMPC ratio if serologic response exists.

Keywords: multiple myeloma, bone marrow, plasma cell ratio, stem cell transplantation

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy. It is originated from monoclonal malignant plasma cells. The peak incidence of MM is in the seventh decade. Significant improvements in prognosis are observed with the addition of many novel agents to treatment options (1-5). Currently, induction therapy with novel agents followed by high-dose melphalan conditioning and autologous stem cell transplantation (ASCT) are considered to be the standard of care in newly diagnosed eligible MM patients (6,7).

Complete remission (CR) in MM is defined as having a <5% bone marrow plasma cell (BMPC) ratio with negative serum and urine immunofixation (IFE) tests (8). Besides, International Myeloma Working Group (IMWG) recommended a more advanced complete remission category described as having normal serum free light chain (FLC) ratio and absence of clonal cells in bone marrow (9). Yet, a few studies were conducted to clarify the significance of BMPC ratio in CR (10-12).

Applying novel agents provided deeper treatment responses and CR rates increased, and the reevaluation of the prognostic effect of achieving CR pre-ASCT became a requisite condition. Kim et al. showed that pre-ASCT CR is an important prognostic factor for better survival. In their study, they assumed all patients with negative serum and urine IFE tests as CR. Bone marrow evaluation was not necessary for patients to be assumed as a CR (12).

In the era of novel agents, there is a need to reevaluate the definition and also the importance of pre-ASCT CR. Besides, it was believed that residual MM cells persisting in the bone marrow despite myeloablative chemotherapy, play a major role in relapse but studies on different purging technics pre-ASCT could not provide a significant non-relapse survival advantage.

Received 14-04-2019 **Accepted** 28-04-2020 **Available Online** 29-04-2020 **Published** 30-04-2020
1 University of Health Sciences, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Dept of Hematology and Bone Marrow Transplantation Center Ankara, TR
*** Corresponding Author:** Semih Başcı **E-mail:** dr.semihbasci@gmail.com

http://dx.doi.org/10.36472/msd.v7i4.372

Therefore it is needed to reveal whether it is really necessary to evaluate pre-ASCT BMPC ratio in patients with measurable monoclonal (M) protein levels at diagnosis and now having a serological treatment response after induction chemotherapy (CR or lower).

In this study, the data of MM patients who underwent ASCT were retrospectively analyzed to find out whether or not the evaluation of pre-ASCT BMPC ratio before had an additional prognostic impact in addition to urine and serum IFE.

Material and Methods

The results of 177 MM patients with measurable M protein levels at diagnosis, underwent ASCT at our center between 2009 and 2018 were analyzed retrospectively. The study was approved by the local ethical committee. The patients' characteristics, myeloma related data and pre-ASCT response are given in Table 1.

Table 1: Patients characteristics

Parameters	Patient Population (n=177)
Age (median)	56 (29-81)
Gender	
Female	69
Male	108
ISS	
ISS I	50
ISS II	53
ISS III	45
Not evaluated	29
Durie Salmon	
DS1	6
DS2	14
DS3	152
Not evaluated	5
Pre-transplantation response	
CR	74
VGPR	45
PR	41
Stable	12
Refractory	5
Chemotherapy line(s)	
1 line	47
2 lines	101
3 lines	22
4 lines	2
5 lines	1
Not evaluated	4
Melphalan	
140mg/m^2	21
200mg/m^2	156
Renal Failure (GFR<50 ml/min)	
Present	9
None	168
Radiotherapy	
Applied	29
None	148
CD34$^+$ cells infused	4.62 x10^6 /kg (2-13,4)

All patients underwent peripheric blood stem cell (PBSC) harvesting. Mobilization of 130 patients were with granulocyte-colony stimulant factor (G-CSF, 10µg/kg), 21 patients were with cyclophosphamide (4.000 mg/m2) plus G-CSF and 6 patients were with plerixafor. 20 patients data regarding mobilization was not available or were applied the non-standard mobilization regimens. Patients older than 70 and/or patients with creatinin higher than 2 mg/dL received lower dose of melphalan 140 mg/m2 as the conditioning regimen, and the other patients received standard dose 200 mg/m2. Patients underwent tandem ASCT were not included in the study.

The overall survival (OS) was termed as the period of time to death or latest follow-up for surviving patients. The progression-free survival (PFS) was termed as the period of time to progression or death or latest follow-up for patients in remission. Engraftment was defined, without any support following 3 days for neutrophil to have absolute neutrophil count (ANC) >500/mm3 and for platelet to have >20000/mm3 (13-17).

Bone marrow aspiration and biopsy were performed before PBSC mobilization. Plasma cell counts were evaluated after CD138 immune staining. To verify the plasma cell, lambda and kappa immune staining were performed. Bone marrow aspiration evaluation was carried out with 500 cell counts.

International Staging System (ISS) and Durie-Salmon Stages (DS) were used staging at diagnosis and treatment response was determined according to the criteria of IMWG (18). Serological CR was described as the absence of identifiable M protein in serum and urine protein electrophoresis (PEP) plus negative IFE.

IBM SPSS Statistics (version 21) was used for statistical analysis. Descriptive statistics were applied to present the data. Categorical data was presented as a ratio, and numerical data was presented as median and mean ± standard deviation. The differences between neutrophil and platelet engraftment times between bone BMPC ratio groups (<5% vs ⩾5%) were investigated by the non-parametric Mann Whitney U test. Chi-square and Fisher exact tests were used to determine the difference between post-transplant response and BMPC ratio groups. Kaplan-Meier survival analysis was applied for PFS and OS and log-rank test were used to examine the factors affecting survival. P values of ⩽0.05 were considered statistically significant.

Results

The 108 (61%) of the 177 MM patients included in the study were females, and 69 (39%) were males. The median age was 56 (range 29-81) and the median disease duration before ASCT was 10 months (range 3-67 months). Median post-transplant follow up was 26 months (range 1 -109 months). Durie-Salmon stages I, II, and III at diagnosis constituted 3.4%, 7.9%, and 85.9% of the patients respectively. 2.8% of the patients' stages at the time of diagnosis could not be reached from the records.

http://dx.doi.org/10.36472/msd.v7i4.372

Before PBSC mobilization, we obtained complete response (CR) in 74 (41.8%) patients, very good partial response (VGPR) in 45 (25.4%) patients and partial response (PR) in 41 (23.2%) patients among 177 patients. According to the immunohistochemical examination of bone marrow biopsy performed before PBSC mobilization, we found 128 (72.3%) patients with bone marrow plasma cell (BMPC) ratio <5% and 49 with (27.7%) ⩾ 5%.

All patients with negative serum and urine IFE were found to have a BMPC ratio <5%. We found that patients with VGPR response, BMPC ratio <5% was in 30 (66.7%) patients and BMPC ratio ⩾5% was in 15 (33.3%) patients. We found among the patients with PR response, BMPC ratio <5% was in 18 (43.9%) patients and BMPC ratio ⩾ 5% was in 23 (56.1%) patients.

The neutrophil and platelet engraftment durations of the patients with pre-ASCT BMPC ratio <5% and BMPC ratio ⩾5% was found similar. In both groups, neutrophil engraftment occurred in median of 11 days whereas platelet engraftment occurred in median of 12 days.

While the transplant-related mortality (TRM) rate was 1.1% among the patients with pre-ASCT BMPC ratio <5% TRM rate was found 0.6% in patients with BMPC ratio ⩾ 5%. No statistically significant difference was found between groups regarding TRM rates (p:0.825).

Among the patients with pre-ASCT BMPC ratio <5%, the post-ASCT response rates were 78.9% CR, 10.2% VGPR and 6.3% PR respectively (4.6% of the patients' post-ASCT response rates could not be reached from the records).

Among the patients with pre-ASCT BMPC ratio ⩾5%, the post-ASCT response rates were 49% CR, 8.2% VGPR, 26.5% PR, 6.1% stable disease, and 6.1% progressive disease respectively (4.1% of the patients' post-ASCT response rates could not be reached from the records).

We found a statistically significant relationship between groups regarding the post-ASCT response rates (p: <0.001*).

Among the patients with BMPC ratio <5% and ⩾5%, the 2-year PFS was 24% and 25% (median PFS 11 months (95% CI; 6,68-15,31) versus 12 months (95% CI; 9,47-14,53)) respectively. No statistically significant relationship was found between the BMPC ratio and PFS post-ASCT (p: 0.900, Fig. 1). Among the patients with BMPC ratio <5% and ⩾5%, the 2-year OS was 67% and 63% (median OS 35 months (95% CI; 25,59-44,41) versus 40 months (95% CI; 27,52-52,47)) respectively. No statistically significant relationship was found between the BMPC ratio and OS post-ASCT (p:0.34, Fig.2).

The patients were divided into 5 groups according to their response rates before transplantation and BMPC ratio (CR and <5% BMPC ratio; VGPR and <5% BMPC ratio; VGPR and ⩾5% BMPC ratio; PR and <5% BMPC ratio; PR and ⩾5% BMPC ratio). When these 5 groups were compared with respect to PFS and OS, we did not find a statistically significant difference among the groups (p=0.439 and p=0.823 respectively) (Table 2).

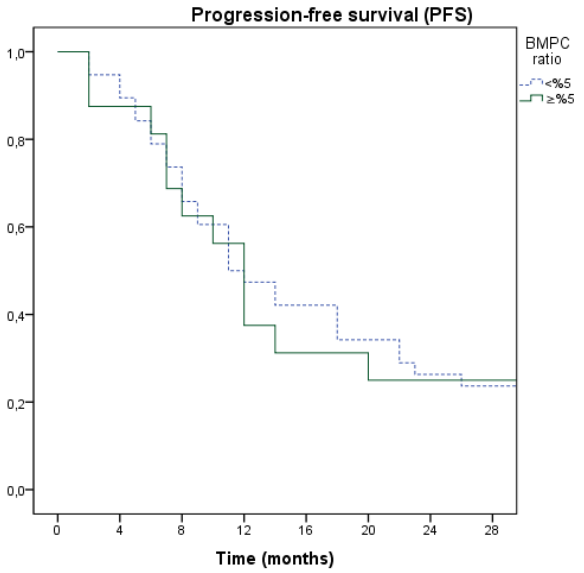

Figure 1: Progression-free survival and Bone Marrow Plasma Cell Ratio

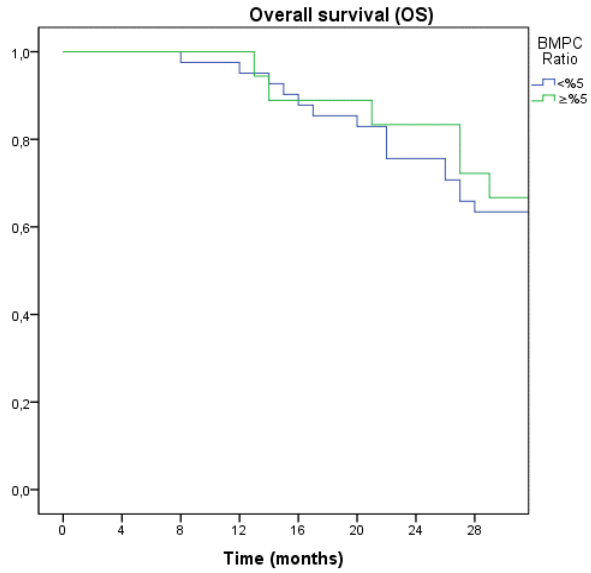

Figure 2: Overall survival and Bone Marrow Plasma Cell Ratio

 http://dx.doi.org/10.36472/msd.v7i4.372

Table 2: The relationship between Pre-transplantation response, Bone Marrow Plasma Cell (BMPC) Ratio and Progression-Free Survival (PFS), Overall Survival (OS)

Pre- transplantation response, Bone marrow plasma cell ratio	n	PFS (months) 95% CI Median(min-max)	OS (months) 95% CI Median(min-max)
CR, BMPC ratio< 5%	74	14 (0,85-27,14)	38 (24,85-51,14)
VGPR, BMPC ratio < 5%	30	11 (6,61-15,38)	33 (15,47-50,53)
VGPR, BMPC ratio ≥ 5%	15	14 (5,41-22,58)	27 (0-79,92)
PR, BMPC ratio < 5%	18	9 (3,86-14,13)	34 (28,15-39,84)
PR, BMPC ratio ≥ 5%	23	8 (2,83-13,16)	40 (26,05-53,94)
P Value		p=0.439	p=0.823

CR: complete remission, VGPR: very good partial remission, PR: partial remission, CI: confidence interval

Discussion

CR is described as having a <5% BMPC ratio in addition to para-protein absence that could be identified with serum and urine IFE negativity lasting for at least 6 weeks (8-12,18-19). However, it is necessary to evaluate whether or not the BMPC ratio should be determined before ASCT in patients MM with measurable disease at diagnosis and have a treatment response after induction therapy. Regression in the initial M protein levels might be enough to indicate chemo-sensitivity in secretory MM patients. Therefore, studies comparing the transplantation outcome of the CR patients and serologically CR with BMPC ratio ⩾5% are required. However, the number of studies conducted on this subject is quite limited. Similarly, studies researching the impacts of BMPC ratios during and after the transplantation in secretory MM patients with serological response are required. In such secretory MM patients, it could be specified whether or not the evaluation of bone marrow plasma ratio is necessarily required along with an absence of M protein in serum and urine IFE or its decrease for the prediction of the ASCT outcome.

In the study conducted by Lee et al. with 106 MM patients, the evaluation of BMPC ratio performed before PBSC mobilization in addition to the serological evaluation with serum and urine IFE on MM patients that underwent ASCT was indicating as a predictor of the disease progression. The prognostic impact of the BMPC ratio has been more evident found out between groups of serological CR and not having a serological CR. Among the patients with not having a serological CR, when the patients with BMPC ratio <5% and ⩾5% were compared, longer PFS and OS were found in patients with BMPC ratio <5% (20). However, in our study, we did not have any patients having a serological CR and BMPC ratio ⩾5% before PBSC mobilization. In the response evaluation conducted before PBSC mobilization, we did not find a statistically significant difference between OS and PFS durations when VGPR and PR response patients were compared after grouped as BMPC ratio <5% and ⩾5%.

These results also suggest that finding a decrease of M protein with serum and urine IFE after an induction treatment of MM patients with measurable disease at diagnosis is sufficient, and the evaluation of the BMPC ratio is not necessarily required.

Because our results indicated that the BMPC ratio evaluation carried out pre-ASCT did not have any impacts on OS and PFS after transplantation. As the BMPC ratio evaluation did not have any impacts on predicting OS and PFS in post-ASCT, its effect on the process of ASCT could not be displayed, either. We did not find any statistically significant difference between the BMPC ratio <5% and ⩾ 5% conducted pre-ASCT with respect to the duration of neutrophil and platelet engraftment and TRM.

Regardless of serological response, the higher CR rate was found in response evaluation after 3 months post-ASCT in patients with pre-ASCT BMPC ratio <5% in comparison to BMPC ratio ⩾5%; however, this did not reflect on PFS and OS.

Conclusion

The number of studies conducted on the impact of the BMPC ratio carried out pre-ASCT on the transplantation outcome is quite limited. In our study, we did not find any impacts of the evaluation of the BMPC ratio before ASCT on the durations of neutrophil and platelet engraftment, TRM rates, and PFS and OS duration in the patients whose M protein were found decreased in the serological test. Limitation of the study was, we did not have any serological CR patients with ⩾5% BMPC ratio, we were unable to evaluate BMPC ratio impacts on serological CR patients. As a conclusion, our study suggests that in MM patients who have measurable disease at diagnosis, it is not required to evaluate the BMPC ratio if serologic response exists.

Author's contributions: Design of the study: **S.B., T.N.Y.**; Literature search: **T.N.Y., M.B.**; Material preparation: **B.U.U. T.D.**; Data collection: **M.B., D.Ş.**; Analysis: **S.B., J.Y.**; Preparation of article and revisions: **S.B., D.İ., N.A.B., T.N.Y.**; Supervision and critical review: **M.K.Ç., M.S.D., F.A.**

Conflict of interest and financial disclosure: The authors declare that there is no conflict of interest and financial relationships.

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

References

1. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood 2008; 111: 2521–2526.

2. Kumar SK, Rajkumar SV, Dispenzieri A et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008; 111: 2516–2520.

3. Kastritis E, Zervas K, Symeonidis A et al. Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG). Leukemia 2009; 23: 1152–1157.

4. Kyle RA, et al. Long-term survival in multiple myeloma. N Engl J Med. 1983; 308(6): 314–316.

5. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21–33.

6. Palumbo A, Cavallo F. Have drug combinations supplanted stem cell transplantation in myeloma? Hematology Am Soc Hematol Educ Program 2012; 2012: 335–341.

7. Harousseau JL. Autologous transplantation for multiple myeloma. Ann Oncol 2008; 19 (Suppl 7): vii128–vii133.

8. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol. 1998; 102(5):1115-1123.

9. Kyle RA and Rajkumar SV, "Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma," Leukemia 2009; vol.23, no.1, pp.3–9.

10. Rajkumar SV, Fonseca R, Dispenzieri A et al., "Effect of complete response on outcome following autologous stem cell transplantation for myeloma," Bone Marrow Transplantation 2000; vol.26, no.9, pp.979–983.

11. Rajkumar SV, Fonseca R, Lacy MQ, et al., "Beta2-microglobulin and bone marrow plasma cell involvement predict complete responders among patients undergoing blood cell transplantation for myeloma," Bone Marrow Transplantation 1999; vol.23, no.12, pp.1261–1266.

12. Kim JS, Kim K, Cheong J-W, Min YH, Suh C, Kim H, et al. Complete Remission Status Before Autologous Stem Cell Transplantation Is an Important Prognostic Factor in Patients with Multiple Myeloma Undergoing Upfront Single Autologous Transplantation. Biol Blood Marrow Transplant [Internet]. 2009; 15(4):463–70.

13. Dreger P, Klöss M, Petersen B et al. Autologous progenitor cell transplantation: prior exposure to stem cell-toxic drugs determines yield and engraftment of peripheral blood progenitor cell but not of bone marrow grafts Blood 1995; 86: 3970-3978

14. Schmitz N, Linch DC, Dreger P et al. Randomized trial of filgrastim-mobilized peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients (erratum: Lancet 1996; 347: 914) Lancet 1996; 347: 353-357

15. Davies SM, Kollman C, Anasetti C et al. Engraftment and survival after unrelated-donor bone marrow transplantation: a report from the national marrow donor program Blood 2000; 96: 4096-4102

16. Bensinger WI, Martin PJ, Storer B et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers New Engl J Med 2001; 344: 175-181

17. Laughlin MJ, Barker J, Bambach B et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors New Engl J Med 2001; 344: 1815-1822

18. Durie BG, Harousseau JL, Miguel JS et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467–1473.

19. Lee S-E, Yahng S-A, Cho B-S, Eom K-S, Kim Y-J, Kim H-J, et al. Lymphocyte subset analysis for the assessment of treatment-related complications after autologous stem cell transplantation in multiple myeloma. Cytotherapy 2012; 14(4):505–512.

20. Lee S-E, Yoon J-H, Shin S-H, Eom K-S, Kim Y-J, Kim H-J, et al. Bone Marrow Plasma Cell Assessment before Peripheral Blood Stem Cell Mobilization in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation. BioMed Research International 2014; Volume 2014, Article ID 982504, https://doi.org/10.1155/2014/982504