Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

# The potential of mononuclear cells as a predictive marker for the level of stem cells in autologous peripheral blood stem cell transplantation in Multiple Myeloma: A Review Article

Darshana Kottahachchi [1*], Tharushika Deshani Hewapathirana [1], Thisali Chandula Perera [1], Shashikala Suresh [2]

1. Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, General Sir John Kotelawala Defence University, Rathmalana, Sri Lanka
2. Department of Haematology Apeksha Hospital, Maharagama, Sri Lanka
* Correspondence: Darshana Kottahachchi. Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, General Sir John Kotelawala Defence University, Rathmalana, Sri Lanka. Tel: +94718023134; Email: darsha.uda@kdu.ac.lk

## Abstract

Multiple myeloma (MM) is a plasma cell neoplasm that is characterized by the clonal proliferation of malignant plasma cells in the bone marrow. It is considered the second most common hematological malignancy which accounts for approximately 1% - 2% of all cancers and among 10% of hematological malignancies. Autologous peripheral blood stem cell Transplantation (PBSCT) is the best treatment for MM. Since the optimum harvested stem cell yield is a crucial factor for sufficient engraftment, the enumeration of Mononuclear cell (MNC) count in peripheral blood and harvested CD 34+ stem cell count can be considered as the best predictive markers for the best timing of apheresis which positively correlates with engraftment outcome of PBSCT.

MNC count can be obtained using either a hematological analyzer or peripheral blood smear while flow cytometry is the advanced technology that can be used to enumerate CD 34+ stem cell count other than peripheral blood smear. The unavailability of a flow cytometer, the expensiveness of this method, and the lack of trained personnel regarding this new technology, especially in lower-middle-income countries cause disturbance in the enumeration of stem cells. In such a situation, this review describes the importance of establishing an association between peripheral blood MNCs and harvested CD 34+ cells. Furthermore, this association facilitates conducting effective PBSCT for MM patients even in the absence of a flow cytometer and eventually, it focuses on decentralizing the treatment of PBSCT.

**Article History**

Received: 14 February 2023
Received in revised form: 27 June 2023
Accepted: 28 February 2024
Published online: 30 April 2024
DOI: 10.29252/mlj.18.2.11

**Keywords**

Multiple myeloma
Stem cells
Autologous transplantation
Plasma cells
Mononuclear cells

**Article Type:** A Review Article



## Introduction

### Multiple Myeloma and epidemiology

Multiple myeloma (MM) is a plasma cell neoplasm that is characterized by the clonal proliferation of malignant plasma cells in the bone marrow (1). It is considered the second most common hematological malignancy (2). Race, radiation exposure, personal history, age, and gender are the risk factors that may influence the development of MM (3). Although this is less common than other types of blood-related cancers, such as leukemia and lymphoma, it occurs most commonly in people over 60 and is slightly more common in men. The average age at diagnosis is 70 and only 2% of cases occur in people under 40 (4). MM accounts for approximately 1-2% of all cancers and about 10% of hematological malignancies in general (2,5).

### Molecular pathology and pathophysiology of MM

MM is associated with malignant plasma cells which are a key part of the immune system. At the immature B cell stage, the rearrangement of immunoglobulin heavy chains and light chains takes place (6-8). This is followed by B cells that transition from bone marrow (BM) into the periphery and secondary lymphoid tissues for maturation. Then CD34+ helper T-cells interaction leads to complex activation of B cells to differentiate into plasma cells in the germinal center that result in the selection of B cells with high-affinity B cell receptors. This process includes somatic alteration termed class switch recombination (CSR) which is more prone to genomic errors during MM (7). During this process, abnormal DNA recombinant events translocate heavy and light immunoglobulin genes to other chromosomes (t (6;14), t (8;14), del(17p), etc.) and generate a malignant phenotype as IgM, IgA, IgG, IgE, IgD myeloma (6-10). Consequently, it inhibits cellular apoptosis, which leads to plasma cells becoming immortalized and continuing to produce an abnormal immunoglobulin (Ig) known as monoclonal immunoglobulin (monoclonal protein, M protein, M spike, Para protein), resulting in monoclonal gammopathy (8).

Then abnormal plasma cells (myeloma cells) produce receptor activators of nuclear factor KB ligand (RANKL) molecules that stimulate osteoclasts for osteolysis which leads to hypercalcemia (11). Abnormal plasma cells create many light chain proteins that form amyloid deposits, which cause renal failure (4). Furthermore, inhibition of normal hematopoiesis can occur by overcrowded bone marrow with myeloma cells. This may lead to anemia and pancytopenia in about 9% of MM patients (2,12,13). Those M proteins secreted by plasma cells can lead to organ damage by causing hyperviscosity syndrome, myeloma nephropathy, and recurrent bacterial infections due to immunocompromised by monoclonal Ig (12,14,15).

### Diagnosis of Multiple Myeloma

### Clinical examination

According to the International Myeloma Working Group criteria, MM can be diagnosed through clinical examination including bone pain, mainly backache caused by the vertebral collapse and pathophysiological fractures, and features of anemia such as lethargy, weakness, dyspnea, pallor, and also give rise to recurrent infections, and tachycardia. The features of renal failure and hypercalcemia, including polydipsia, polyuria, vomiting, anorexia, constipation, and mental disturbance, also can be seen. Amyloidosis occurs in 5% with features such as carpal tunnel syndrome, macroglossia, and diarrhea, and a few cases (2%) with hyperviscosity syndrome with purpura hemorrhages, CNS symptoms, visual failure, and heart failures (12,16).

### Laboratory investigations

In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for MM to diagnose MM during symptomatic and asymptomatic stages (15). Clinicians frequently requested laboratory investigations to screen for MM are complete blood count (Hemoglobin < 10 g/dL, or > 2 g/ dL below the lower limit of normal), WBC and platelets (normal or lower normal), ESR (very high; 160-180mm/h), serum protein such as total protein, serum beta 2 microglobulin and immunoglobulin, serum calcium (very high) and Bence Jones protein may present in the urine. Other biochemical investigations such as renal function tests including serum creatinine (> 2 mg/dL) or creatinine clearance (< 40 mL/min) higher than the upper limit of normal or > 2.75 mmol/L) can be used for further screening (5,16).

Under the major diagnostic criteria, the examination of BM aspiration and trephine biopsy can be used to identify myeloma cells and their distribution (>20% of plasma cells in the bone marrow). The BM aspiration is used for other tests such as immunohistochemistry, chromosome analysis, including karyotype and fluorescent in situ hybridization (also known as FISH), and flow cytometry to ensure the cause of MM (17). Monoclonal M protein on serum/urine electrophoresis and immunofixation can be used for qualitative and quantitative diagnosis of the exact type of abnormal type of immunoglobulin in MM (18).

Over 80% of abnormal plasma cells in plasma cell disorders produce monoclonal immunoglobulin (Ig) and free light chains. The serum free light chain assay (sFLC) is used to quantify the abnormal concentration of free light chains in serum (kappa and lambda). In MM, either one type of kappa or lambda chain extremely increases in the serum in relation to the other type. It leads to an extreme increase or decrease in the ratio of kappa to lambda (0.26-1.76), which is an indication of MM (19). Due to the short half-life of FLC (2-6 hours compared to IgG), sFLC can be used for early monitoring of the effectiveness of the therapies and diagnosis of MM (18,20). The major application of sFLC assay in monitoring and diagnosing MM, which secretes only LC, is known as Bence Jones MM. According to the studies conducted by Bradwell et al. (2003) and Katzman et al. (2002), sFLC concentration has a greater correspondence to tumor level compared to Bence Jones protein in the urine (21,22). Evaluating the ratio of FLC in IgD type MM makes it possible to monitor the response to the therapies (23). Average about only 70% of Non-secretory MM cases are produced monoclonal LC, which assay useful in monitoring and relapse state of this disorder (15). Imaging tests such as X-ray, magnetic resonance imaging (MRI), low-dose whole-body CT (computed tomography), or fluorodeoxyglucose-

positron emission tomography (FDG-PET) for better detection of bone and extramedullary disease may be recommended to detect bone problems associated with MM (4,11).

**Treatments for Multiple Myeloma**

According to clinical practice guidelines in oncology, treating multiple myeloma depends on age, performance status, comorbidities, and whether the patient is symptomatic with the current relapse (24). Treatments for multiple myeloma are divided into specific (chemotherapy and radiotherapy) and supportive (17).

**Chemotherapy**

The non-transplant candidates are treated with melphalan-based novel combination regimens (Melphalan, Prednisolone, Thalidomide). Most frequently, two-drug combination regimens of chemotherapy such as thalidomide with dexamethasone (TD), lenalidomide with low dose dexamethasone (Rd), bortezomib with dexamethasone (BD) are administrated to the MM patients (25). According to a study related to treatments for MM, it reflects 65%-75% of the rate of responses provided by TD (25). However, it is not the drug of choice recently because toxicity and the early mortality rate are high with TD. Still, focusing on increasing efficiency and reducing the toxicity with the patient dosage seems prudent.

**Radiotherapy**

According to the study by Talamo et al. (2015), two-thirds of MM patients require radiation therapy to destroy the multiplication of cancer cells by targeting their DNA (26). The authors observed about 75%- 100% range of pain control with radiation therapy. Most patients have significant loss of pain by treating 3000cGy in fractions of 10 to 15.

**Other treatments**

Targeted therapy of MM includes novel agents known as immunomodulatory drugs. Proteasome inhibitor, bortezomib, is the drug of choice. The study by Anderson et al. (2018) concluded that pamidronate, zoledronic acid and denosumab can use as bone-modifying drugs (27). Denosumab can be considered superior to zoledronic acid for the prevention of skeletal-associated events. The article by Geraldes et al. (2021) reflects that the food and drug administration recommended daratumumab as a treatment for MM (28). This immune-modulating drug can use alone or combine with other drugs taken to treat other types of MM, such as daratumumab plus hyaluronic acid. This study was performed including 66 patients, and among them, 84.8% responded to this treatment.

**Stem cell transplantation**

Thirty years after the work of Powles, Barlogie, and McElwain led to the initiation of the concept of high-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT). Transplantation remains the standard for treating newly diagnosed multiple myeloma patients. According to Bladé et al. (2010), ASCT should be considered whenever possible in MM patients with sensitive relapse (29). In this study, they have published five randomized trials which compare the ASCT against high dose chemotherapy by involving the population of 2411 patients undergoing ASCT and conventional chemotherapy treatment (30). Two trials reflected significantly increased complete remission (CR) rate, event-free survival (EFS), and overall survival (OS). The other 3 trials showed no significance of ASCT in EFS and OS. The Intergroup Francophone du Myeloma (IFM) reported prolonged survival by 10 months with tandem (double) transplantation and the OS is about seven years (29). Currently, stem cells are used as standard therapy for patients with malignancies such as certain leukemias, MM, and lymphomas. They promote the repair response of diseased, dysfunctional, or injured body tissue. It is described as hemopoietic stem cell transplantation (HSCT) (31). In HSCT, there are two types of transplantation: bone marrow transplantation (BMT) and peripheral blood stem cell transplantation (PBSCT) (32). These two treatments are performed to replace cells destroyed by radiotherapy or chemotherapy and restore normal BM function. Autologous and allogenic are the methods of performing stem cell transplantation (32). In the past, allogenic transplantation was used to treat congenital immune deficiency, certain leukemias, myelodysplastic syndrome (MDS), and also beta-thalassemia patients (33). In such conditions, stem cells are obtained from identical donors, siblings or parents. If not, then choose a relevant donor after typing the HLA. Graft versus host disease (GVHD) is considered the main adverse effect of allograft transplantation (31). Hence, autologous transplantation is more applicable to treating MM.

**Autologous stem cells as standard treatment for Multiple Myeloma**

The study conducted by Lisenko et al. (2017) reflects that ASCT was introduced to give some protection to the BM when patients receive high-dose chemotherapy. ASCT is performed mainly for myeloma and lymphomas and to treat difficult autoimmune disorders as well (34). In this method, stem cells are collected from the same patient, and performing HLA typing is unnecessary (30). Stem cells are preserved and administered to the same patient after a high dose of chemotherapy to complete the transplant (31). It has a lower risk of life-threatening complications. However, there is still a possibility of GVHD occurring (35).

**Process of Autologous Peripheral Blood Stem Cell Transplantation (PBSCT)**

According to previous studies related to transplantation the first source of stem cells is BM. Stem cells are detached from the bone marrow microenvironment and released into circulation and returned to the BM (31). Therefore, this study reflects that peripheral blood is a convenient source of stem cells, and uses of PBSCT rather than bone marrow transplantation (BMT). The autologous stem cell transplantation process contains five stages such as stem cell mobilization, the collection of stem cells, processing and storage, conditioning, and finally reinfusion (30).

Before the collection of blood cells, a mobilizing agent is given to the patient to collect PBSC. Filgrastim and lenograstim are used as the main G-CSF cytokines as mobilizing agents. Other than that, for chemo mobilization, cyclophosphamide is used. A combination of chemotherapeutic agents and G-CSF are more likely to yield optimal HSC harvest than those mobilized by G-CSF alone. But nowadays plerixafor chemotactic drug is used for proper mobilization, minimizing side effects and enhancing the harvesting time (36).

Stem cells are collected from patients using an apheresis machine (FC500 Beckman Coulter, Spectra Optia Apheresis system-Terumo BCT machine) other components of blood cells are returned to the patients' bodies (37).

According to the study conducted by Allan et al. (2002) once the stem cells are collected, they need to be processed immediately or should be stored at $4^0$C overnight following the addition of 50ml of autologous plasma (38). Then the sample is centrifuged to make a stem cell concentrated cell product. The concentrated cell pack is diluted with 2 parts of M199 tissue culture media, 2 parts of patient plasma and 1 part of DMSO then cryopreserved (frozen) at -$196^0$C in liquid nitrogen. As a result, stem cells remain viable for at least 10 years (38).

The conditioning regimen is started within a few days to a few weeks after their collection, patients go through a high dose of IV chemotherapy for the complete elimination of myeloma cells (39). The first conditioning regimen is high-dose cyclophosphamide combined with total body irradiation (TBI). Pancytopenia and nonhematologic side effects will happen as a result of conditioning therapy (30).

The harvested stem cells are given back to the patient through an intravenous catheter a day or two after chemotherapy treatment as planned (40). After the re-infusion of stem cells into the bloodstream, they start to migrate to the BM and begin to produce new cells in a few days and will become normal in two and three weeks after transplant. This process is known as engraftment which is successful when the absolute neutrophil count is $0.5\times10^9$/L. There is low immunity from conditioning to engraftment due to the production of a low number of blood cells (41). Hence, Autologous PBSCT can improve the survival of multiple myeloma patients for at least five years (42). Moreover, several factors affect an individual's survival, such as overall health and age (42).

**Mononuclear cells and method of enumeration**

During the harvesting of stem cells, the hemopoietic stem cells concentrate into a buffy coat after centrifugation as they are having high density. This product contains stem cells, myeloid precursors, monocytes, and lymphocytes which are collectively called mononuclear cells (MNC) (39,40).

**Enumeration using Peripheral Blood Smears**

The study conducted by Krishnan et al. (2021) used a manual differential count of 200 cells performed by using Wright-stained smears of PBSC product under an oil immersion field to determine MNCs (43). Then they expressed MNC count as a percentage of the total leukocyte count which was obtained by the sum of the percent of monocytes, lymphocytes, and progenitor cell population. Accordingly, the absolute MNC count was derived from the total leukocyte count. At present, some underdeveloped countries in the absence of flow cytometers use peripheral blood smears to estimate MNC (44,45).

**Enumeration using hematological analyzers**

Ahmed et al. (2020) conducted a correlation study to evaluate the MNC count based on different hematology analyzers (5- part and 3-part) and emphasized a good correlation between the 5-part hematology analyzer with the manual gold standard method of MNC count indicating equivalent performance (45). They also showed that MNC can be performed by 5-part with no significant difference and can be used as well as manual count (46). But with the advancement in technology, automated hematological analyzers (Eg; Mindray BS 6800, Sysmex, Erba H360 etc.) and flow cytometers (Beckman Coulter, Sysmex, BD Biosciences, Luminex etc.) are used to count those MNCs in the peripheral blood.

**Stem cells and the methods of enumeration**

Stem cells are the type of biological unspecialized cells found in almost all multicellular organisms, which are capable of self-renewal over long periods and differentiate into specialized cell types (potency) (47). There are mainly three types of stem cells, namely embryonic, adult, and fetal stem cells which can be divided further into pluripotent, multipotent, totipotent, unipotent, and oligopotent (47,48). The stem cells that are found in peripheral blood or the bone marrow are called hematopoietic stem cells (HSC) which are multipotent. They have the potency to differentiate into myeloid and lymphoid cells (49), and give rise to various hematopoietic cells such as platelets, erythrocytes, granulocytes, monocyte/macrophages, T, B cells, and NK cells (50).

The harvested PBSC obtained during the process of apheresis can be quantitatively determined by using flow cytometry with the help of CD34+ markers on the cells or by using stem cell culture (39,48), and then it determines the potency of hemopoietic stem cell products. Therefore, almost all hematopoietic pluripotent and committed stem cells in colony-forming assays express CD34 (51).

The International Society of Hematotherapy and Graft Engineering (ISHAGE) has validated the flow cytometric method for the quantitative determination of CD34+ cells in peripheral blood and apheresis products using

stem cell kit (52). Hence, flow cytometry (Beckman Coulter, Sysmex, BD Biosciences, Luminex etc.) can be used to detect the potency of hemopoietic stem cell products. The CD34+ hemopoietic stem cell sample is stained with fluorescently labeled antibodies against stem cell antigens, CD34+, and then excited by the laser to emit light at varying wavelengths. Then the number of CD34+ in the sample is determined by the amount of emitted fluorescence. (53) For deciding the optimal time of collection by apheresis and for effective auto hemopoietic stem cell transplantation, treatment with an accurate quantification of CD34+ is required. The reasonable cutoff of CD34 for an effective PBSCT collection is ≥10-20×$10^3$/ml (54). The studies conducted by Park et al. (2001) and Yu et al. (2016) showed that a harvest of >2×$10^6$ CD34+ cells/kg of body weight is generally considered to be the minimum requirement for stable hematological engraftment (54,55). Moreover, >5×$10^6$ CD34+ cells/kg which is defined as an optimal hemopoietic stem cell harvested is associated with faster hematological recovery.

Concerning correlations between MNC counts and CD 34+ yield over the decade, many efforts have been made to find helpful parameters to predict the optimal time for initiating efficient PBSC collection (48,56). The peripheral white blood cell (WBC), percentage of circulating immature cells of granulocytic lineage, the lymphocyte count and monocyte count have previously been considered an indicator of the optimum day for harvesting. Plenty of literature exists on peripheral blood MNCs and CD34+ level as reliable predictive markers for SCT (57,58). However, an association between those parameters is scarce. The current flow cytometric techniques used to measure CD34+ cells are expensive and labor intensive, and the unavailability of the flow cytometer in some underdeveloped countries and lack of technical knowledge cause disturbance when estimating the stem cell yield.

In such a situation, finding an association between mononuclear cell count in peripheral blood and stem cell count using CD34+ can reduce unnecessary wastage of blood products with effective SCT, even in the absence of flow cytometry. The circulating MNC in peripheral blood after mobilization is used to predict the optimal time for initiating an efficient PBSC yield as the ability of PBSCT to produce rapid engraftment depends on the number of CD34+ cells infused. Bhat et al. (2019) conducted a study to assess the CD34+ hematopoietic progenitor cells enumerated by flow cytometry and the utility of performing MNC count before performing the stem cell enumeration and they were able to perform counts directly from the leukapheresis pack and see the reliability of this practice. They reported that the MNC counts > 4 x $10^8$ /pack/kg correlated well with the CD34+ hematopoietic progenitor cells of > 2 x$10^6$ per pack/kg body weight suggesting it was a crude method for assessing the mobilization (52). Research has consistently demonstrated a strong correlation between peripheral CD34 levels and apheresis CD34 levels. This correlation suggests that peripheral CD34 levels serve as a reliable predictor for initiating stem cell collection, particularly in the context of transplantation (59). However, a separate study conducted by Hewapathirana et al. in 2023 focused on peripheral blood MNCs and CD34+ levels. Their findings emphasized a weaker correlation between peripheral MNCs and apheresis CD34 levels. Despite this weaker association, they could derive a specific cutoff value for MNCs. They aimed to demonstrate that MNC could still be effectively used as a predictive marker to determine CD34 counts during the apheresis process (60).

The correlations between MNC counts and CD 34+ yield in the peripheral blood obtained by various research groups using aforesaid techniques are summarized in Table 1 (43,57,60).

**Table 1.** Studies comparing correlations between MNC counts and CD 34+ yield in PBSC product.

| Research group | Material | Peripheral Blood Components | | Techniques employed |
|---|---|---|---|---|
| | | MNC count | CD34 count | |
| Bhat et al. (2019) DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20190346 | PBSC product | ≥4×$10^8$/kg | ≥2×$10^6$/kg | Flow cytometry (Beckman coulter Navios ,2 laser and 8 color instrument) Beckman coulter LH 750 hematological analyzer Peripheral blood smear |
| Krishnan et al. (2021) DOI: 10.4103/ajts.AJTS_21_2 Website: www.ajts.org | Peripheral blood | ≥2×$10^6$/kg | ≥60/µl | Flow cytometry Peripheral blood smear |
| | PBSC product | ≥3.4×$10^8$/kg | 2×$10^6$/kg | Sysmex automated analyzer |
| Zhang et al. (2008) DOI: 10.1016/j.transci.2008.05.011 | Peripheral blood | 5.06 ± 1.50 ×$10^8$/kg | 2.45 ± 0.76×$10^6$/kg | Flow cytometry (FACScan, Becton Dickinson) |

## Conclusion

In this review, we discussed the PBSCT as the treatment of choice for multiple myeloma. Furthermore, we reviewed the attempts that has been made by the various research groups to establish an association between peripheral blood MNCs and harvested CD 34+ cells using flow cytometer. Establishing such an association facilitates conducting effective PBSCT for MM patients even in the absence of flow cytometry and it eventually enables to decentralize the treatment of PBSCT. Finally, this aids in reducing laboratory limitations and achieving better resource management on apheresis by preventing unnecessary procedures and costs. Moreover, there is a need to focus on the type of automated hematology analyzer (Eg; Mindray BS 6800, Sysmex, Erba H360 etc.) and the type of flow cytometer (Beckman Coulter, Sysmex, BD Biosciences, Luminex etc.) when establishing a correlation that specific to the type of analyzer to overcome the variations. Moreover, if we can establish correlations between automated hematology analyzer and manual method in enumeration of MNC, we will be able to decentralize the treatment of PBSCT even in the absence of automated methods. The objective is thus, to achieve the feasibility of quantifying MNC cells in peripheral blood before the apheresis to improve the success rate of apheresis collection in local samples of patients with a higher turnaround.

## Acknowledgement

The authors would like to thank General Sir John Kotelawala of Defence University, Sri Lanka, for the support provided in all aspects.

## Funding sources

Not applicable

## Ethical statement

Not applicable

## Conflicts of interest

The authors declare that there is no conflict of interest.

## Author contributions

All authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission.

## References

1. Devenney B, Erickson C. Multiple myeloma: an overview. Clinical Journal of Oncology Nursing. 2004;8(4):401-5. [View at Publisher] [PMID] [Google Scholar]
2. Sridevi HB, Rai S, Suresh PK, Somesh MS, Minal J. Pancytopenia in Multiple Myeloma- An Enigma: Our Experience from Tertiary Care Hospital. J Clin Diagn Res. 2015;9(11):EC04-6. [View at Publisher] [Google Scholar]
3. Ternák G, Berényi K, Németh B, Szenczi Á, Márovics G, Kiss I. Association of antibiotic-consumption patterns with the prevalence of hematological malignancies in European countries. Sci Rep. 2022;12(1):7821. [View at Publisher] [PMID] [Google Scholar]
4. Bell D, Yap K. Multiple myeloma. Radiopaedia.org. 2010. [View at Publisher] [DOI]
5. Kazandijan D. Multiple myeloma epidemiology and survival, a unique malignancy. Semin Oncol. 2016;43(6):676-81. [View at Publisher] [DOI] [PMID] [Google Scholar]
6. Giudicessi JR, Ackerman MJ. Determinants of incomplete penetrance and variable expressivity in heritable cardiac arrhythmia syndromes. Transl Res. 2013;161(1):1-14. [View at Publisher] [DOI] [PMID] [Google Scholar]
7. Tonon G. Molecular Pathogenesis of Multiple Myeloma. Hematol Oncol Clin North Am. 2007;21(6):985-1006. [View at Publisher] [DOI] [PMID] [Google Scholar]
8. Chng WJ, Glebov O, Bergsagel PL, Kuehl WM. Genetic events in the pathogenesis of multiple myeloma. Best Pract Res Clin Haematol. 2007;20(4):571-96. [View at Publisher] [DOI] [PMID] [Google Scholar]
9. Agnarelli A, Chevassut T, Mancini EJ. IRF4 in multiple myeloma-Biology, disease and therapeutic target. Leuk Res. 2018;72:52-8. [View at Publisher] [DOI] [PMID] [Google Scholar]
10. Lodé L, Eveillard M, Trichet V, Soussi T, Wuillème S, Richebourg S, et al. Mutations in TP53 are exclusively associated with del(17p) in multiple myeloma. Haematologica. 2010;95(11):1973-6. [View at Publisher] [DOI] [PMID] [Google Scholar]
11. Hoffbrand AV, Pettit JE, Moss PAH. Essential Haematology (Essentials). 4th Edition. Wiley-Blackwell Paperback. (2001) [View at Publisher]
12. Subramanian R, Basu D, Dutta TK. Prognostic significance of bone marrow histology in multiple myeloma. Indian J Cancer. 2009;46(1):40-5. [View at Publisher] [DOI] [PMID] [Google Scholar]
13. Dispenzieri A, Gertz MA, Therneau TM, Kyle RA. Retrospective cohort study of 148 patients with polyclonal gammopathy. Mayo Clin Proc. 2001;76(5):476-87. [View at Publisher] [DOI] [PMID] [Google Scholar]
14. NORD (National Organization for Rare Disorders). Multiple Myeloma. 2022;1-5. [View at Publisher]

15. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003;121(5):749-57 [View at Publisher] [PMID] [Google Scholar]
16. Rajkumar SV. Updated Diagnostic Criteria and Staging System for Multiple Myeloma. Am Soc Clin Oncol Educ B. 2016;36:e418-23. [View at Publisher] [DOI] [PMID] [Google Scholar]
17. Samson D, Singer C. Multiple myeloma. Clin Med (Northfield Il). 2001;1(5):365-70. [View at Publisher] [DOI] [PMID] [Google Scholar]
18. Palumbo A, Rajkumar SV, San Miguel JF, Larocca A, Niesvizky R, Morgan G, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol. 2014;32(6):587-600. [View at Publisher] [DOI] [PMID] [Google Scholar]
19. UCSF Helen Diller Family Comprehensive Cancer Center. About Multiple Myeloma. 2022. [View at Publisher]
20. Pratt G, Mead GP, Godfrey KR, Hu Y, Evans ND, Chappell MJ, et al. The tumor kinetics of multiple myeloma following autologous stem cell transplantation as assessed by measuring serum-free light chains. Leuk Lymphoma. 2006;47(1):21-8. [View at Publisher] [DOI] [PMID] [Google Scholar]
21. Bradwell AR, Carr-Smith HD, Mead GP, Harvey TC, Drayson MT. Serum test for assessment of patients with Bence Jones myeloma. Lancet. 2003;361(9356):489-91. [View at Publisher] [DOI] [PMID] [Google Scholar]
22. Katzman M, George T, Doell H, Danyluk P, Briggs S, Hasegawa W, et al. Combination High-Dose Cyclophosphamide and Bortezomib Is Safe and Effective for Stem Cell Harvesting in Chemotherapy Refractory Multiple Myeloma. Blood. 2006;108(11):5459. [View at Publisher] [DOI] [Google Scholar]
23. Fonseca R, Bergsagel PL, Drach J, Shaughnessy J, Gutierrez N, Stewart AK, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leuk 2009 2312 [Internet]. 2009 Oct 1 [cited 2022 Mar 23];23(12):2210-21. [View at Publisher] [DOI] [PMID] [Google Scholar]
24. Raje NS, Anaissie E, Kumar SK, Lonial S, Martin T, Gertz MA, et al. Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group. Lancet Haematol. 2022;9(2):e143-61. [View at Publisher] [DOI] [PMID] [Google Scholar]
25. Rajkumar SV. Treatment of multiple myeloma. Nat Rev Clin Oncol [Internet]. 2011;8(8):479-91. [View at Publisher] [DOI] [PMID] [Google Scholar]
26. Talamo G, Dimaio C, Abbi KKS, Pandey MK, Malysz J, Creer MH, et al. Current role of radiation therapy for multiple myeloma. Front Oncol. 2015;5(FEB):40. [View at Publisher] [DOI] [PMID] [Google Scholar]
27. De la Puente P, Muz B, Azab F, Luderer M, Azab AK. Molecularly targeted therapies in multiple myeloma. Leuk Res Treatment. 2014;2014:976567. [View at Publisher] [DOI] [PMID] [Google Scholar]
28. Geraldes C, Neves M, Chacim S, da Costa FL. Practical Considerations for the Daratumumab Management in Portuguese Routine Clinical Practice: Recommendations from an Expert Panel of Hematologists. Front Oncol. 2022;11:817762. [View at Publisher] [DOI] [PMID] [Google Scholar]
29. Bladé J, Rosiñol L, Cibeira MT, Rovira M, Carreras E. Hematopoietic stem cell transplantation for multiple myeloma beyond 2010. Blood. 2010;115(18):3655-63. [View at Publisher] [DOI] [PMID] [Google Scholar]
30. Léger CS, Nevill TJ. Hematopoietic stem cell transplantation: A primer for the primary care physician. Cmaj. 2004;170(10):1569-77. [View at Publisher] [DOI] [PMID] [Google Scholar]
31. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med. 2006;354(17):1813-26. [View at Publisher] [PMID] [Google Scholar]
32. Shimosato Y, Tanoshima R, Tsujimoto SI, Takeuchi M, Shiba N, Kobayashi T, Ito S. Allogeneic Bone Marrow Transplantation versus Peripheral Blood Stem Cell Transplantation for Hematologic Malignancies in Children: A Systematic Review and Meta-Analysis. Biol Blood Marrow Transplant. 2020;26(1):88-93. [View at Publisher] [DOI] [PMID] [Google Scholar]
33. Passweg JR, Baldomero H, Bader P, Bonini C, Duarte RF, Dufour C, et al. Use of haploidentical stem cell transplantation continues to increase: the 2015 European Society for Blood and Marrow Transplant activity survey report. Bone Marrow Transplant. 2023;52(6):811-7. [View at Publisher] [DOI] [PMID] [Google Scholar]
34. Lisenko K, Sauer S, Bruckner T, Egerer G, Goldschmidt H, Hillengass J, et al. High-dose chemotherapy and autologous stem cell transplantation of patients with multiple myeloma in an outpatient setting. BMC Cancer. 2017;17(1):151. [View at Publisher] [DOI] [PMID] [Google Scholar]
35. Hutchinson K, Kopko PM, Muto KN, Tuscano J, O'Donnell RT, Holland PV, et al. Early diagnosis and successful treatment of a patient with transfusion-associated GVHD with autologous peripheral blood progenitor cell transplantation. Transfusion. 2002;42(12):1567-72. [View at Publisher] [DOI] [PMID] [Google Scholar]
36. Al Hamed R, Bazarbachi AH, Malard F, Harousseau JL, Mohty M. Current status of autologous stem cell transplantation for multiple myeloma. Blood Cancer J. 2019;9(4):44. [View at Publisher] [DOI] [PMID] [Google Scholar]
37. Asia Pacific Hospice Palliative Care Network. Cancer Care Association. 2022. [View at Publisher]
38. Allan DS, Keeney M, Howson-Jan K, Popma J, Weir K, Bhatia M, et al. Number of viable CD34(+) cells reinfused predicts engraftment in autologous hematopoietic stem cell transplantation. Bone Marrow Transplant. 2002;29(12):967-72. [View at Publisher] [DOI] [PMID] [Google Scholar]
39. Gyurkocza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not fit all. Blood. 2014;124(3):344-53. [View at Publisher] [DOI] [PMID] [Google Scholar]
40. Garderet L, Beohou E, Caillot D, Stoppa AM, Touzeau C, Chretien ML, et al. Upfront autologous stem cell transplantation for newly diagnosed elder ly multiple myeloma patients: A prospective multicenter study. Haematologica. 2016;101(11):1390-7. [View at Publisher] [DOI] [PMID] [Google Scholar]
41. Bolaman AZ, Turgutkaya A, Yavaşoğlu İ. Factors Affecting Time to Engraftment During Autologous Stem Cell Transplantation in Patients with Multiple Myeloma. Plasmatology. 2021;15. [View at Publisher] [DOI] [Google Scholar]
42. Gerecke C, Fuhrmann S, Strifler S, Schmidt-Hieber M, Einsele H, Knop S. The Diagnosis and Treatment of Multiple Myeloma. Dtsch Arztebl Int. 2016;113(27-28):470-6. [View at Publisher] [DOI] [PMID] [Google Scholar]
43. Krishnan A, Murugesan M, Therayangalath B, Philip KJ, Nayanar SK, Nair CK. Determination of mononuclear cell count using peripheral smear and flow cytometry in peripheral blood stem cell products: A retrospective study from an Indian cancer center. Asian J Transfus Sci. 2021;15(2):151-6. [View at Publisher] [DOI] [PMID] [Google Scholar]
44. Kleiveland CR. Peripheral Blood Mononuclear Cells. In: Verhoeckx K, Cotter P, López-Expósito I, Kleiveland C, Lea T, Mackie A, Requena T, Swiatecka D, Wichers H, editors. The Impact of Food Bioactives on Health: in vitro and ex vivo models [Internet]. Cham (CH): Springer; 2015. Chapter 15. [View at Publisher] [DOI] [PMID] [Google Scholar]
45. Sheikh BA, Mehraj U, Bhat BA, Hamdani SS, Nisar S, Qayoom H, et al. Immunoglobulin. Basics Fundam Immunol [Internet]. 2022 Jan 24 [Cited 2022 Apr 11]:139-74. [View at Publisher]
46. Rundgren IM, Ersvær E, Ahmed AB, Ryningen A, Bruserud Ø. Circulating monocyte subsets in multiple myeloma patients receiving autologous stem cell transplantation - a study of the preconditioning status and the course until posttransplant reconstitution for a consecutive group of patients. BMC Immunol. 2019;20(1):39. [View at Publisher] [DOI] [PMID] [Google Scholar]
47. Ahmed R, Ganguli P, Gupta UD, Jaiswal YK, Nair V, Das S, et al. Mononuclear cell evaluation: A correlation study between manual and analyzer-based estimation. Biomed Biotechnol Res J. 2020;4(1):34-40. [View at Publisher] [DOI] [Google Scholar]
48. Pura Krishnamurthy K, Sarathy V, Jayappa SB, Badarkhe GV, Kumar Ks R, Thianeshwaran S, et al. Study of Peripheral Mononuclear Cells and CD34 Levels as a Predictive Marker for Initiating Apheresis in Autologous Stem Cell Transplant. Int J Hematol Oncol Stem Cell Res. 2021;15(3):170-7. [View at Publisher] [PMID] [Google Scholar]
49. Bonig H, Papayannopoulou T. Hematopoietic stem cell mobilization: updated conceptual renditions. Leukemia. 2013;27(1):24-31. [View at Publisher] [DOI] [PMID] [Google Scholar]
50. Gardner RL. Stem cells: potency, plasticity and public perception. J Anat. 2002;200(Pt 3):277-82. [View at Publisher] [DOI] [PMID] [Google Scholar]
51. Adolfsson J, Månsson R, Buza-Vidas N, Hultquist A, Liuba K, Jensen CT, et al. Identification of Flt3+ Lympho-Myeloid Stem Cells Lacking Erythro-Megakaryocytic Potential: A Revised Road Map for Adult Blood Lineage Commitment. Cell. 2005;121(2):295-306. [View at Publisher] [DOI] [Google Scholar]
52. Bindu H, Stem Cell Res Ther J, Bindu HA. Potency of Various Types of Stem Cells and their Transplantation. J Stem Cell Res Ther. 2011;1:115. [View at Publisher] [DOI]
53. Lemos NE, Farias MG, Kubaski F, Scotti L, Onsten TGH, Brondani LA, et al. Quantification of peripheral blood CD34+ cells prior to stem cell harvesting by leukapheresis: a single center experience. Hematol Transfus Cell Ther. 2018;40(3):213-8. [View at Publisher] [DOI] [PMID] [Google Scholar]
54. Naeim F, Nagesh Rao P, Song SX, Grody WW. Chapter 2 - Principles of Immunophenotyping. Atlas of Hematopathology (Second Edition). 2018;29-56. [View at Publisher] [DOI]
55. Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I. The ISHAGE guidelines for CD34+ cell determination by flow cytometry. International Society of Hematotherapy and Graft Engineering. J Hematother. 1996;5(3):213-26. [View at Publisher] [DOI] [PMID] [Google Scholar]

56. Matarraz S, Almeida J, Flores-Montero J, Lécrevisse Q, Guerri V, López A, et al. Introduction to the diagnosis and classification of monocytic-lineage leukemias by flow cytometry. Cytometry B Clin Cytom. 2017;92(3):218-27. [View at Publisher] [DOI] [PMID] [Google Scholar]
57. Yu JT, Cheng S Bin, Yang Y, Chang KH, Hwang WL, Teng CLJ. Circulating hematopoietic progenitors and CD34+cells predicted successful hematopoietic stem cell harvest in myeloma and lymphoma patients: Experiences from a single institution. J Blood Med. 2016;7:5-11. [View at Publisher] [DOI] [PMID] [Google Scholar]
58. Park KU, Kim SH, Suh C, Kim S, Lee SJ, Park JS, et al. Correlation of hematopoietic progenitor cell count determined by the SE-9000TM automated hematology analyzer with CD34+ cell count by flow cytometry in leukapheresis products. Am J Hematol. 2001;67(1):42-7. [View at Publisher] [DOI] [PMID] [Google Scholar]
59. Pahwa D, Sharma RR, Marwaha N. Predictors of Mononuclear Cell Yield in Patients Undergoing Autologous Mononuclear Stem Cell Therapy in Non-haemopoietic Degenerative Disorders. Indian J Hematol Blood Transfus. 2018;34(2):282-93. [View at Publisher] [DOI] [PMID] [Google Scholar]
60. Bhat S, Hussain S, Noor H, Shoket N. CD34+ hematopoietic progenitor cells enumeration and mononuclear cell count: an experience from a tertiary care centre. Int J Res Med Sci. 2019;7(2):421. [View at Publisher] [DOI] [Google Scholar]

**How to Cite:**
Kottahachchi D, Hewapathirana TD, Perera TC, Suresh S. The potential of mononuclear cells as a predictive marker for the level of stem cells in autologous peripheral blood stem cell transplantation in Multiple Myeloma: A Review Article. *Med Lab J.* 2024;18(2):11-5.