Plasma Cell Contamination in Autografts Determined by Dual Quantification Before Cryopreservation and After Thawing Predicts Transplant Outcomes in Multiple Myeloma: A Prospective, Proof-of-Concept Study

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What is already known on this topic?

- *Higher volumes of clonal plasma cells measured in autologus grafts before cryopreservation is associated with earlier relapse after transplantation*

What this study adds on this topic?

- *A repeat measurement of plasma cell content in the autograft after cryopreservation and thawing is a simple and feasible method to potentially enhance the prognostic accuracy of measuring plasma cell contamination in autografts*

Abstract

Objective: Plasma cell contamination in freshly collected autografts has been rigorously investigated as a marker to identify patients at a high risk of progression after autologous stem cell transplantation (ASCT), with conflicting results. The association between the plasma cell content in thawed autografts and clinical outcomes is yet to be studied.

Methods: This was a prospective cohort study; viable plasma cell content in autografts was quantified by flow cytometry both before cryopreservation and after thawing to evaluate its correlation with transplant outcomes. Multiple myeloma patients undergoing their first ASCT were enrolled. Patients were stratified into a low- or high-plasma cell contamination group with a predefined 2:1 ratio based on combined data from both time-point measurements. The primary endpoint was progression-free survival (PFS) based on plasma cell contamination of autografts.

Results: Forty-nine patients were included in this primary analysis with a median follow-up of 36 months. The median age was 57, and key baseline features were evenly distributed between the 2 groups. High-plasma cell contamination group had a significantly increased risk of progression or death after ASCT (3-year PFS: 31.3% vs. 74.7%, hazard ratios (HR)= 6.36, $P < .0001$), independent of International Staging System (ISS), response state, age, and genetic features on multivariate analysis (HR = 8.9, $P < .0001$). The predefined stratification based on data from both time-point cell counts outperformed correlations based on single time-point measurements for predicting PFS. Twenty-eight of 49 patients were found to have more than a 50% reduction in plasma cell/stem cell ratio in the autograft after thawing. These 28 cases had a significantly lower risk of progression or death after ASCT compared to the remaining 21 cases (HR = 0.38, $P = .042$).

Conclusion: This is the first study to evaluate post-thaw autograft plasma cell content as a risk factor for ASCT failures. Findings support its clinical relevance and encourage further studies to incorporate this potential marker into predictive models.

Keywords: Autologous transplantation, cancer, multiple myeloma, plasma cells

Introduction

The standard management of medically fit patients diagnosed with multiple myeloma (MM) consists of induction therapy followed by autologous stem cell transplantation (ASCT).[1-5] This sequence of initial management has remained similar for over 2 decades, despite tremendous developments in the field with novel targeted drugs.[1,3,6-10] The efficacy, tolerability, and expanding diversity of the therapeutic

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armamentarium have advanced to such a degree that the role and optimal timing of ASCT are increasingly subject to debate.[9-13]

A fraction of patients progress early after ASCT and face the consequences of its toxicities without deriving any benefit.[6,14,15] This subset of patients has been difficult to identify, and outcomes have most consistently been correlated with the depth of response to frontline therapy or genetic aberrations.[14,16-18] Despite significant developments in the treatment landscape, early transplant failures are still feared, and reliable identification of patients unlikely to benefit specifically from ASCT remains an evolving area of research.[15,18,19]

Contamination of autologous grafts with malignant plasma cells has intrigued researchers as a potential mechanism for relapse after ASCT.[20-25] Some studies have found significant correlations between flow cytometric evidence of a high number of plasma cells in autografts with inferior clinical outcomes.[21,25-28] Studies that evaluated autograft purging have reported conflicting results[29,30] and autograft plasma cell content has not been validated as a robust variable for predictive modeling.[1,18,19]

Autografts used for ASCT undergo routine processing before they are infused, including the addition of Dimethyl sulfoxide (DMSO), exposure to extreme cold temperatures, and thawing.[31] The previous studies quantified plasma cells exclusively prior to cryopreservation.[21,23,25,26,30,32] Considering that plasma cells can be sensitive to in-vitro manipulations,[33,34] it was hypothesized that a second plasma cell quantification after thawing may provide additional information and contribute to an ASCT-specific predictive model. To test this hypothesis, a single-center prospective cohort study was conducted. Its findings will be described and discussed in this paper.

Methods

This was designed as a prospective, observational study at a single transplant center. All MM patients undergoing first, single ASCT were consecutively included on the day of the first leukapheresis.

The in-house protocols for ASCT in MM, practiced for over 20 years, included stem cell quantification by flow cytometry immediately before cryopreservation and on the day of the transplant after thawing. For this study, cell surface markers for CD38 and CD138 were added to the routine flow cytometric preparation of autograft samples.

For the quantification of stem cells and plasma cells in the autografts, a 50µL sample was counted in the Siemens Beckman Coulter automatic hematology analyzer for total leukocytes per mm^3. Another 10µL sample was incubated for 15 minutes at 2-8°C, protected from light after the addition of antibodies, CD45 ECD (2 µL), CD34 FITC (3 µL), 7-AAD PC5 (2 µL), CD38 PE (2.5 µL), and CD138 KrO (3 µL). Following the first incubation, ammonium chloride (0.5 mL) was added for erythrocyte lysis and the sample was incubated for an additional 7 minutes. This prepared mixture was run through the multicolor flow cytometry device Beckman Coulter Navios Ex V2.0 (10 colors, 3 lasers), targeting 500,000 events for each sample. The Kaluza C software was used for the processing and analysis of flow cytometric data. Viable cells were gated initially at the time-SS plots. Stem cells were quantified in accordance with the ISHAGE protocol (Figure 1). Plasma cells were quantified by 2 researchers (TE, MÇ), both highly experienced in operating and analyzing flow cytometry. The 2 operators of flow cytometric output were not blinded to each other and only 1 plasma cell/stem cell ratio was documented per measurement after a consensus was reached between the 2 operators. Plasma cells and stem cells within the sample were quantified and recorded immediately. Following a planned preliminary analysis of flow cytometric data from the first 10 cases, the plasma cell-to-stem cell ratio was designated as the primary parameter for assessing plasma cell contamination. Plasma cell/stem cell ratio was preferred over absolute plasma cell counts to facilitate the development of a simplified, user-friendly predictive model. The rationale was based on the fact that stem cell doses are routinely

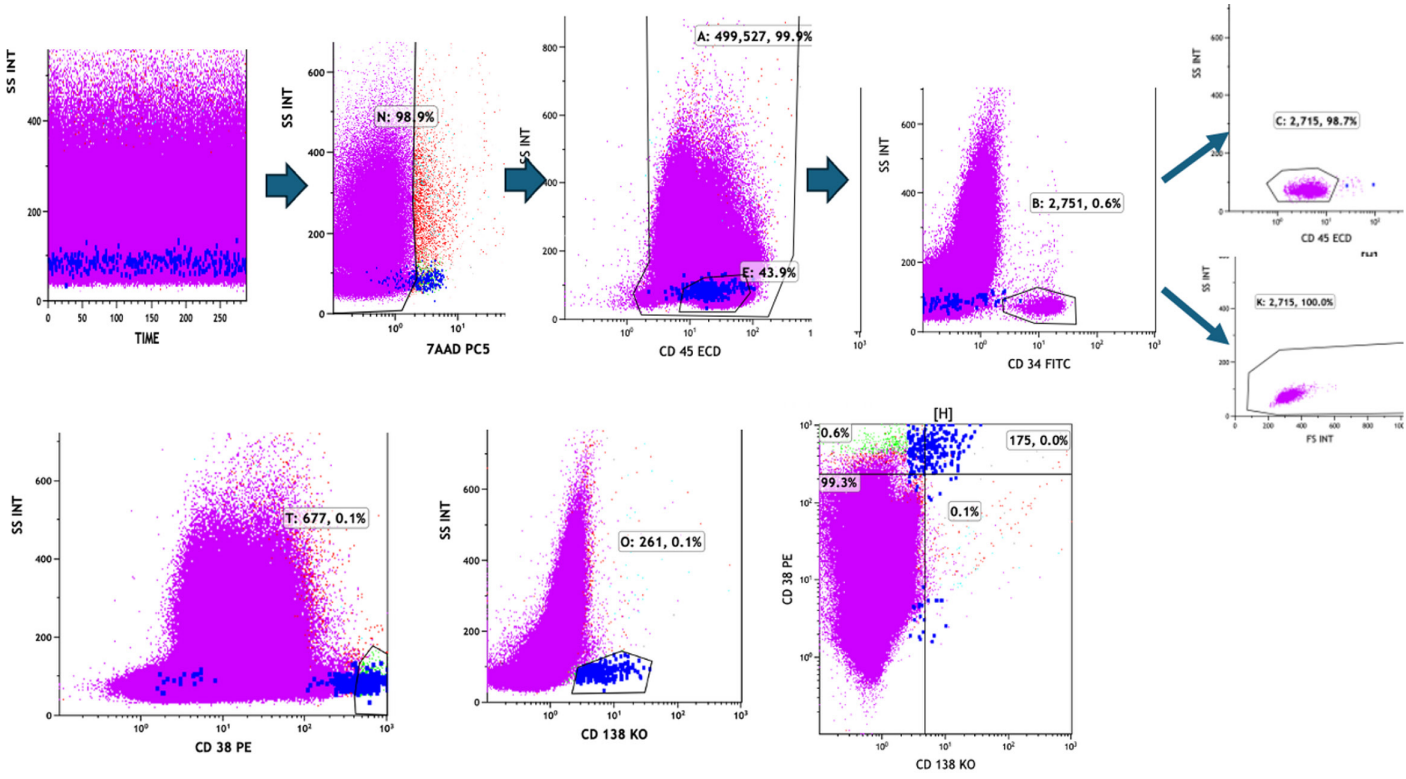

Figure 1. Flow cytometric diagrams of 1 subject, demonstrating steps and gating for stem cell and plasma cell quantification.

adjusted according to patient body weight and maintained within a narrow range of 2.5–5 × 10^6 cells/kg, whereas plasma cell counts exhibited substantial inter-patient variability. For confirmatory purposes, the absolute numbers of stem cells and plasma cells in each autograft were also calculated using leukocyte counts obtained from an automated hematology analyzer in conjunction with the total autograft volume. The same quantification procedure was repeated on the day of ASCT using a sample from the thawed autograft, and all measurements were systematically recorded.

The primary endpoint of the study was progression-free survival (PFS) in relation to the plasma cell contamination of the autograft. Secondary endpoints included PFS stratified by plasma cell/stem cell ratio at each measurement and based on a decrement (50%) of the plasma cell/stem cell ratio from pre-cryopreservation to post-thaw.

The ratio of plasma cells to stem cells in the autograft was predefined to stratify patients into groups for the analyzed endpoints. Regarding the primary endpoint, "plasma cell contamination" in the autograft was predefined in the study protocol as a composite function of both measurements before cryopreservation and after thawing, with the aim of categorizing patients into low and high levels of contamination with a 2:1 ratio. This stratification was formulated in 2 steps. First, patients with an autograft plasma cell/stem cell ratio within the top 66th percentile in the measurement pre-cryopreservation were selected. Among this subset, those with a post-thaw plasma cell/stem cell ratio above the median were classified as the high plasma cell contamination group. The remaining cases were assigned to the low plasma cell contamination group. The primary analysis was planned after a median follow-up of 36 months.

Statistical Analysis

Based on retrospective data from the same center, a 50% rate of PFS events was assumed within 3 years of ASCT.[17] In alignment with the predefined 2:1 stratification ratio, a sample size of 60 patients was calculated to correspond to an 80% power to significantly detect a hazard ratio of 3 for the group of patients with a high-plasma cell contaminated autograft using a 2-tailed alpha level of 5%.

Background data was presented with descriptive statistics using frequency and the median. Response states and progression were defined in accordance with the IMWG 2014 criteria.[34] Progression-free survival was defined as the time from ASCT to documentation of disease progression or death. Patients without a PFS event were censored at the time of the last clinical visit. The Kaplan–Meier method was used to generate time-to-event plots. Hazard ratios (HR) were calculated by Cox regression to determine statistical significance in survival analyses. High-risk genetic anomalies were defined as (+1q, t(4,14), t(14,16), del 17p). The multivariate analysis was modeled based on univariate analysis results, with individual variables of potential association to post-transplant PFS ($P <$ .2) included in the final multivariate model. The CI was 95% for all statistical analyses, considering 2-sided P values <.05 significant. IBM-SPSS version 20 was used for statistical analysis.

Ethics Statement

All patients signed informed consent for the anonymous use of their medical data for research purposes. The study received ethical approval from the institutionalİstanbul University-Cerrahpaşa Clinical Research Ethical Board on July 6th, 2021 (Approval No: E-83045809-604.01.02-133973, Confirmation Code: BSVHT8PCU2). No patient photo, radiological image, or any potential individual identifier was used in the preparation of this manuscript.

Results

Patients were enrolled between 2021 and 2023, and recruitment was prematurely terminated following the February 6, 2023, earthquakes in Türkiye, which led to the temporary closure of the transplant unit for up to 1 year to support urgent operational needs. Outpatient follow-up was continued regularly. Overall, 52 patients were initially enrolled following leukapheresis. However, 2 patients succumbed to COVID-19 infection after stem cell collection, before receiving ASCT. The flow cytometric readout of 1 patient did not meet the quality standards and was excluded from analysis. As a result of these exclusions and early termination of patient recruitment, 49 patients were included in the follow-up and primary analysis of this study.

The median age was 57 years; all patients had undergone leukapheresis within 2 months from the end of induction therapy, and there was a slight male predominance (Table 1). Only 2 patients received chemo-mobilization, and the remaining 47 received growth factor with or without plerixafor for stem cell collection. Baseline characteristics, including ISS stage, genetic aberrations, age, paraprotein type, extent of bone marrow infiltration, and the number of infused stem cells, were evenly distributed between the 2 groups stratified by plasma cell contamination in the autograft (Table 1). Bortezomib-cyclophosphamide-dexamethasone (VCD) was the first-line regimen in all but 3 cases, who received bortezomib-lenalidomide-dexamethasone (VRD). Second- and third-line regimens were administered to 61.2% and 16.3% of patients, respectively, before ASCT. All patients received at least 3 cycles of bortezomib-based regimens (VCD-VRD), and 61.2% received at least 3 cycles of lenalidomide-containing regimens, which included combinations with either bortezomib, carfilzomib, or daratumumab. Deeper responses were slightly more common in the group with lower plasma-cell contamination; however, the vast majority had a very good partial remissiom or better response at the time of ASCT in both groups and received lenalidomide maintenance (Table 1).

Regarding the primary endpoint, 33 patients were classified into the low-plasma cell contamination group and 16 were classified into the high plasma cell contamination group based on the predefined 2:1 stratification ratio. All patients in the high-contamination group exhibited a plasma cell-to-stem cell ratio exceeding 1:29 in both pre-cryopreservation and post-thaw measurements. In contrast, for the low-plasma cell contamination group, the plasma cell/stem cell ratio was below this threshold in 25 of 33 pre-cryopreservation and all post-thaw measurements. After a median follow-up of 36 months, the 3-year PFS was 74.7% vs. 31.3% in favor of the low-plasma cell contamination group. This translated to a significantly increased risk for disease progression or death for the high-plasma cell contamination group with a HR of 6.36 (95% CI = 2.3-17.7, $P <$ .0001, Figure 2a). The difference was similar when patients not receiving lenalidomide maintenance (n = 9) were excluded (HR = 6.27, P = .004). Preliminary univariate analyses to generate a multivariate model revealed a potential association of ISS (HR = 1.61, P = .099), response state before ASCT (HR = 2.29, P = .07), high-risk genetics (HR = 1.88, P = .19), and age (HR = 1.18, P = .18) with post-transplant PFS. These were included in the multivariate model. Lenalidomide maintenance (HR = 0.58, P = .27), number of lines of therapy before ASCT (HR = 0.87 P = .64), number of infused stem cells per weight (HR = 0.96 P = .84), gender (HR: 0.98. P = .96), and bone marrow plasma cell ratio at diagnosis (HR = 0.97, P = .45) were not considered potentially associated with post-transplant outcomes and were excluded from the multivariate model. Plasma cell contamination was independent of ISS, response state, high-risk genetic anomalies, and age in multivariate Cox regression analysis (Figure 2b).

Table 1. Selected Baseline Features, Response Rates, Mobilization Data, Cell Counts, Post-transplant Management Across the Entire Cohort and Between the 2 Groups Based on Plasma Cell Contamination in Autografts

Feature	Study Cohort (n = 49)	High Plasma Cell Contamination (n = 16)	Low Plasma Cell Contamination (n = 33)
Median age (IQR)[a]	57 (49-64)	60 (53-62)	56 (47-64)
Female/Male (n/n)	20/29	7/9	13/20
ISS 1 ISS 2 ISS 3	34.1% 29.5% 36.4%	37.6% 31.2% 31.2%	32.1% 28.6% 39.3%
IgG type myeloma[a] Kappa/Lambda	51% 1.58	56.2% 1.67	48.5% 1.54
Bone marrow infiltration >50%[a] High-risk cytogenetics[b]	51% %18.4	43.7% 18.7%	54.5% 18.2%
Response CR/VGPR[c] Response PR[c]	83.7% 14.3%	75% 18.7%	87.7% 12.3%
Plerixafor use	30.6%	31.2%	30.3%
Median plasma/stem cell ratio in graft before cryopreservation	1/23.2	1/6.1	1/46.3
Median plasma/stem cell ratio in graft after thawing	1/27	1/10.2	1/118.6
Median no. of stem cells infused x10⁶/kg (IQR)	3.4 (2.9-4.75)	3.3 (2.8-4.7)	3.4 (3-4.8)
Median no. of days from apheresis to ASCT (IQR)	31 (24-60)	38 (28-60)	29 (24-60)
Mel200/Mel140	45/4	14/2	32/2
Engraftment (median day, IQR)	+10 (10-11)	+10 (10-11)	+10 (10-11)
Lenalidomide maintenance	81.6%	81.8%	81.2%

[a]At the time of diagnosis.
[b]t(4,14), t(14,16), +1, del17p.
[c]Last evaluation before mobilization.
ISS; International Staging System, ASCT, autologous stem cell transplantation; CR, complete remission; IQR interquartile range; Mel200, melphalan 200mg/m2; Mel140, melphalan 140mg/m2; PR, partial remission; VGPR, very good partial remissiom.

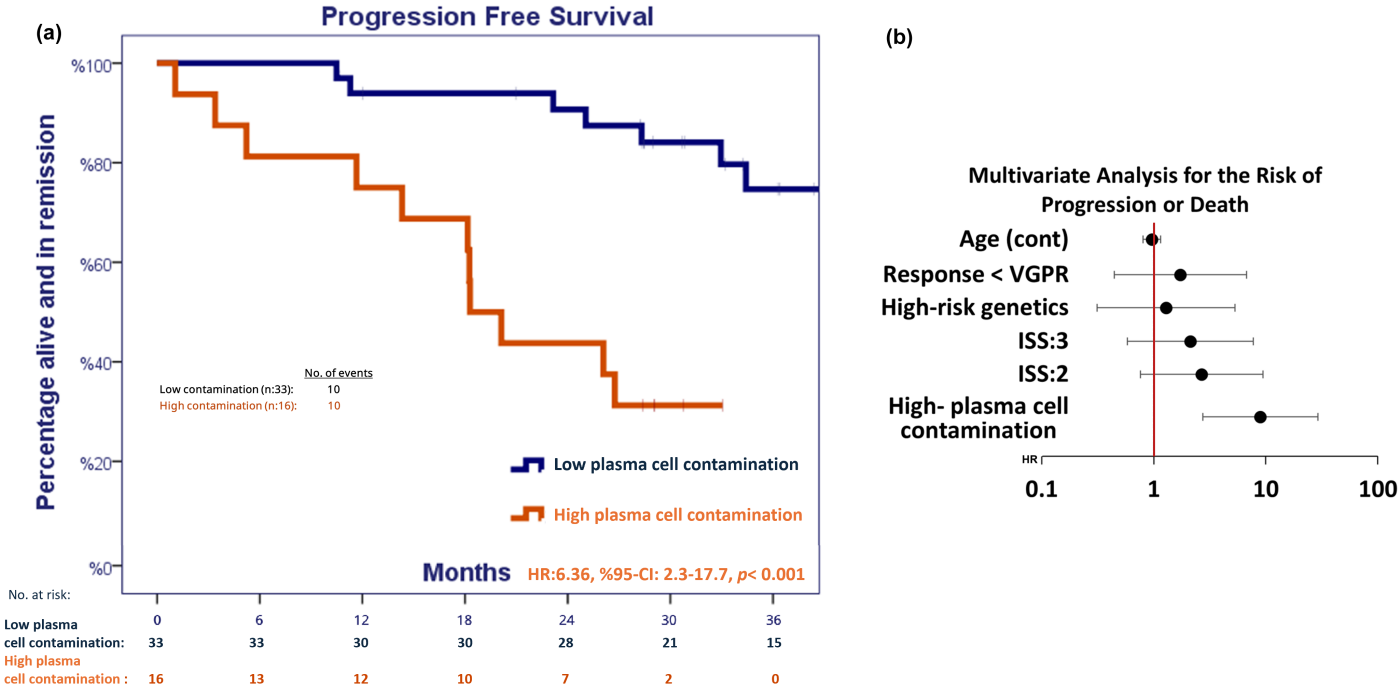

Figure 2. Kaplan Meier curve. (a) comparing groups of patients based on the level of plasma cell contamination defined by information from both measurements before cryopreservation and after thawing. Forest plot (b) demonstrating hazard ratio and 95% confidence interval for the risk of progression or death based on multivariate Cox regression analysis.

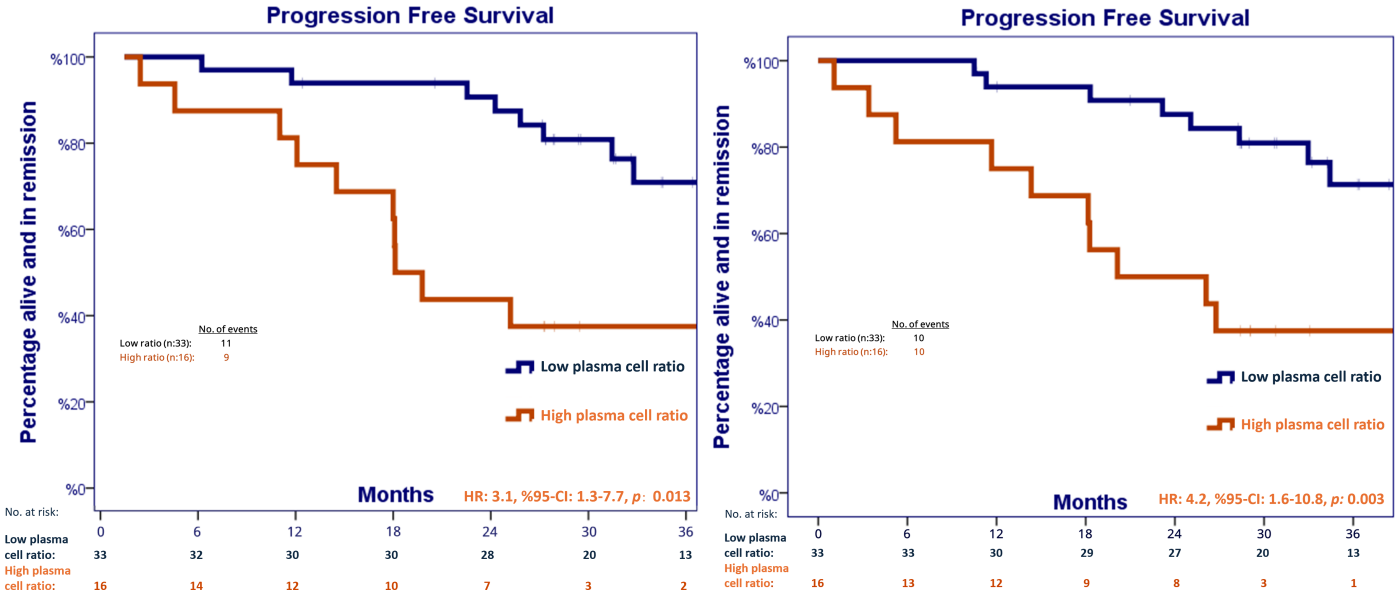

Figure 3. Kaplan Meier curves comparing patients based on the ratio of plasma cells/stem cells quantified before cryopreservation (a) and after thawing (b.

Plasma cell/stem cell ratios as single measurements before cryopreservation or after thawing were also found to significantly correlate with PFS; however, the separation of curves was less pronounced compared to stratification based on combined data from both measurements. The HR for progression or death was 3.1 (95% CI = 1.3-7.7, *P* = .013, Figure 3a) and 4.2 (95% CI = 1.6-10.8, *P* = .003, Figure 3b) for patients in the highest 33rd percentile in measurements before cryopreservation and after thawing, respectively.

As an exploratory endpoint, a significant reduction (>50%) in the plasma cell/stem cell ratio between the pre-cryopreservation and post-thaw measurements was observed in 28 of 49 cases. Upon further analysis, viable stem cell counts were within 8.4% of the initial values, indicating that the observed decline in the ratio was attributable to the decrease in plasma cell viability following the in-vitro manipulations, including the addition of DMSO, cryopreservation, and thawing. The 2-year PFS was 85.4% versus 61.9%, favoring the 28 patients with more than 50% decline in

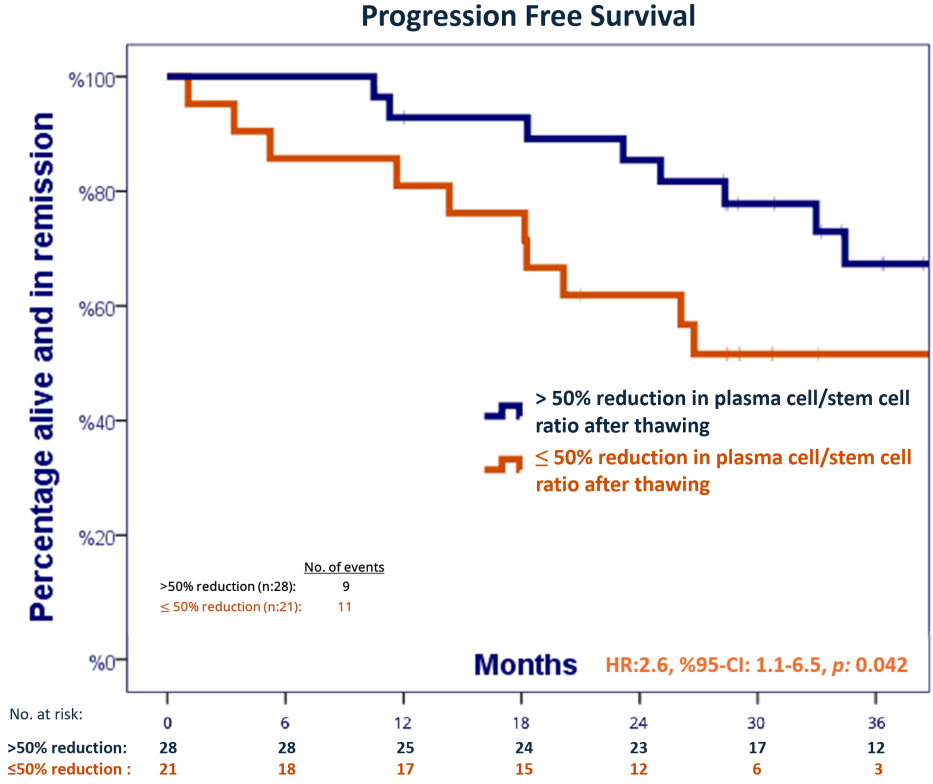

Figure 4. Kaplan Meier curves comparing PFS based on the decline of the plasma cell/stem cell ratio from the measurement before cryopreservation to the measurement post-thaw.

plasma cell/stem cell ratio after thawing (HR = 2.6, 95% CI = 1.1-6.5, *P*= .042, Figure 4).

Discussion

This paper presents the primary analysis of a prospective cohort study, investigating the predictive accuracy of autograft plasma cell contamination for ASCT outcomes in MM. Measuring plasma cells in thawed autografts was a novel method authentic to this study. Forty-nine patients were included, and after a 36-month median follow-up from ASCT, patients classified to the high-plasma cell contamination group demonstrated a significantly increased risk of progression or death. While the plasma cell/stem cell ratios at single time-point measurements, either before cryopreservation or after thawing, were correlated with outcomes, the predefined stratification using combined data from both time-point measurements outperformed single measurements as a predictor of transplant outcomes. Importantly, high levels of plasma cell contamination of the autograft were found independent of established markers, including ISS, response state, and genetic aberrations as a risk factor for progression. Patients transplanted with autografts measured to have a plasma cell count decline of over 50% after thawing, compared to the count before cryopreservation, were found to have a 62% lower risk of progression.

As the therapeutic landscape in MM expands, optimizing predictive models specific to ASCT outcomes is becoming increasingly relevant in clinical practice to refine the sequencing of therapies.[1,3,6,8,9,14,16,35-39] While there is a trend to position novel therapies at earlier lines, financial concerns and the availability of long-term data support the place of more traditional options such as ASCT following induction.[1,3,6,7,35,38] Ideally, precise predictive models identifying cases least likely to benefit from traditional therapies should guide the administration of innovative approaches in earlier lines. While poor response to induction therapy and the presence of high-risk genetic anomalies are currently the most widely recognized features for unfavorable ASCT outcomes,[18,19] recent studies revived the interest in autograft plasma cell contamination as a prognostic indicator.[27,28] One of these studies demonstrated that aberrant plasma cells detected in autografts were associated with a lower probability of achieving complete remission or measurable residual disease (MRD) negativity.[27] The other, more recent study found that the plasma cell measurements in autografts combined with bone marrow MRD information improved prediction based on bone marrow MRD alone concerning ASCT outcomes.[28] Both studies observed contemporary cohorts receiving targeted induction therapies and evaluated autografts before cryopreservation. The findings complement these reports and propose a practical and less expensive method to define plasma cell contamination, while introducing the concept that a repeat measurement after thawing may provide additional useful information as a predictive marker.

The findings of this study provide a proof-of-concept for a repeat plasma cell quantification of the autograft following completion of all in vitro manipulations, at the point when cells are ready for infusion. The method used for plasma cell measurement was simplified, incorporating only 2 additional markers beyond the routine stem cell quantification protocols. Furthermore, the targeted number of events in flow cytometry was kept at 500,000, substantially lower than the multiple-million events used in earlier studies.[27,28] This simple method did not allow differentiation between malignant and normal plasma cells, limiting the precision of measurements. Nevertheless, the study tested a novel approach incorporating a second measurement to compensate for the simplicity of the method and arrived at encouraging results, which can be useful when advanced methods are unavailable. The interpretation of results is limited by the relatively small sample size, single-center design, and the operator-dependent nature of the flow cytometric readout, necessitating local expertise. The 2 flow cytometry operators were not blinded to each other's calculations, and a lack of analysis for interobserver variability can be considered a limitation. However, due to the simplicity of the employed methods and the use of only 2 cell-surface markers, the calculations were considered straightforward and significant interobserver variability was not reported. The early termination of patient enrollment limited the sample size to 82% of the predefined target. However, this did not jeopardize the study endpoints as the differences in survival comparisons were more pronounced than the initial assumptions, yielding significant correlations. Nonetheless, the findings require validation from larger, multi-center studies before a standardized plasma cell/stem cell ratio threshold for stratification can be established. Furthermore, due to the small sample size, the multivariate analysis should be interpreted with caution since the study was not powered to evaluate the performance of ISS, response state at ASCT or genetic features on predicting transplant outcomes. The absence of MRD data or plasma cell clonality assessment in autografts represents a limitation; however, the study prioritized feasibility, aiming to offer a broadly applicable and accessible methodology. The biological nature of observed differences in the reduction of plasma cell counts between measurements could not be determined explicitly with the methods used in the study and deserves further exploration in future studies.

To the best of current knowledge, this is the first study to prospectively evaluate plasma cell content of the post-thaw autograft as a predictor of ASCT outcomes. Using a simple method, the study found promising correlations that encourage further investigation with post-thaw autograft plasma cell counts. Subsequent studies confirming the reproducibility of these findings can promote autograft plasma cell content as a marker of a robust predictive model specific for ASCT outcomes with potential implications for risk-stratification in clinical research and ultimately for treatment sequencing in clinical practice.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Istanbul University-Cerrahpaşa (Approval No.: E-83045809-604.01.02-133973; Date: 06.07.2021).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

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Search – U.Y., M.B., T.E., A.S.; Writing Manuscript – U.Y., T.E.; Critical Review M.C.A., A.S.

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