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Autologous

Optimizing Autologous Stem Cell Transplantation in Multiple Myeloma: The Impact of Intensive Chemomobilization

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Most transplant-eligible multiple myeloma (MM) patients undergo autologous peripheral blood stem cell collection (PBSC) using G-CSF with on-demand plerixafor (G ± P). Chemomobilization (CM) can be used as a salvage regimen after G ± P failure or for debulking residual tumor burden ahead of autologous peripheral blood stem cell transplantation (ASCT). Prior studies utilizing cyclophosphamide-based CM have not shown long-term benefits. At our center, intensive CM (ICM) using a PACE- or HyperCVAD-based regimen has been used to mitigate "excessive" residual disease based on plasma cell (PC) burden or MM-related biomarkers. Given the lack of efficacy of non-ICM, we sought to determine the impact of ICM on event-free survival (EFS), defined as death, progressive disease, or unplanned treatment escalation. We performed a retrospective study of newly diagnosed MM patients who collected autologous PBSCs with the intent to proceed immediately to ASCT at our center between 7/2020 and 2/2023. Patients were excluded if they underwent a tandem autologous or sequential autologous-allogeneic transplant, had primary PC leukemia, received non-ICM treatment (i.e., cyclophosphamide and/or etoposide), or had previously failed G ± P mobilization. To appropriately evaluate the impact of ICM among those who potentially could have received it, we utilized a propensity score matching (PSM) approach whereby ICM patients were compared to a cohort of non-CM patients matched on pre-ASCT factors most strongly associated with the receipt of ICM. Of 451 patients identified, 61 (13.5%) received ICM (PACE-based, n = 45; hyper-CVAD-based, n = 16). Post-ICM/pre-ASCT, 11 patients (18%) required admission for neutropenic fever and/or infection. Among 51 evaluable patients, the overall response rate was 31%; however, 46 of 55 evaluable patients (84%) saw a reduction in M-spike and/or involved free light chains. Among those evaluated with longitudinal peripheral blood flow cytometry (n = 8), 5 patients (63%) cleared circulating blood PCs post-ICM. Compared to patients mobilized with non-CM, ICM patients collected a slightly greater median number of $CD34^+$ cells (10.8 versus 10.2 × 10^6/kg, P = .018). The median follow-up was 30.6 months post-ASCT. In a PSM multivariable analysis, ICM was associated with significantly improved EFS (hazard ratio [HR] 0.30, 95% CI 0.14 to 0.67, P = .003), but

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not improved OS (HR 0.38, 95% CI 0.10 to 1.44, P = .2). ICM was associated with longer post-ASCT inpatient duration (+4.1 days, 95% CI, 2.4 to 5.8, $P < .001$), more febrile days (+0.96 days, 95% CI 0.50 to 1.4, $P < .001$), impaired platelet engraftment (HR 0.23, 95% CI 0.06 to 0.87, P = .031), more bacteremia (OR 3.41, 95% CI 1.20 to 9.31, P = .018), and increased antibiotic usage (cefepime: +2.3 doses, 95% CI 0.39 to 4.1, P = .018; vancomycin: +1.0 doses, 95% CI 0.23 to 1.8, P = .012). ICM was independently associated with improved EFS in a matched analysis involving MM patients with excessive disease burden at pre-ASCT workup. This benefit came at the cost of longer inpatient duration, more febrile days, greater incidence of bacteremia, and increased antibiotic usage in the immediate post-ASCT setting. Our findings suggest that ICM could be considered for a subset of MM patients, but its use must be weighed carefully against additional toxicity.

INTRODUCTION

In the era of quadruplet therapy, most transplant-eligible patients with multiple myeloma (MM) achieve excellent disease control following induction and autologous hematopoietic stem cell transplantation (ASCT) [1]. However, a subset of patients with aggressive disease still have a suboptimal response. Achieving a complete response in the pre- or post-ASCT setting is clearly associated with superior prognosis [2-6], yet treatment intensification before ASCT for patients who fail to achieve a deep response has been poorly studied in the modern era. The Myeloma XI trial explored a risk-adapted strategy, assessing the efficacy of response-adapted intensification to a second induction line. While this approach demonstrated improved progression-free survival, it is important to note that the study utilized outdated regimens that are no longer commonly employed in current clinical practice [7]. In the pre-ASCT setting, a CIBMTR registry study found that additional post-induction standard chemotherapy-based salvage therapy improved the depth of response but did not impact long-term outcomes [8].

Most ASCT-eligible patients undergo stem cell collection using G-CSF with on-demand plerixafor (G ± P), though the use of chemomobilization (CM) has been evaluated as an alternative strategy to debulk tumor burden immediately prior to ASCT. Unfortunately, cyclophosphamide-based CM has repeatedly failed to demonstrate significant cytoreductive capacity and has no demonstrable impact on long-term outcomes [9-14]. Given its associated toxicities and increased utilization of resources, the use of cyclophosphamide-based CM is not routinely recommended [10].

However, there is a paucity of evidence regarding the effectiveness of intensive CM (ICM) strategies that involve multi-drug regimens incorporating drugs to which the disease has not been previously exposed. Our group previously examined the use of an ICM strategy with KRD-PACE (carfilzomib, lenalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide) among 27 MM patients with "excessive" residual disease burden. These patients tended to have the following pre-ASCT disease characteristics: the presence of circulating blood plasma cells (PCs) detected by flow cytometry, bone marrow PCs (BMPCs) ≥10% per IHC pathology review, a serum monoclonal protein ≥1 gram per deciliter (g/dL), and/or an involved serum free light chain (FLC) ≥10 milligrams per deciliter (mg/dL) [11]. Increasing derangement of each of these parameters has been shown by others to portend worse long-term outcomes [5,15-21]. The objective response rate of the ICM regimen in our initial publication was 50% among evaluable patients. However, nearly half of the patients experienced grade 3/4 nonhematologic toxicity, and a quarter required unplanned re-admission due to toxicity. Long-term outcomes were not available at the time of the initial publication [11].

We now report on the long-term outcomes of MM ASCT patients who received pretransplant ICM therapy. In light of the advancement in myeloma therapies, and prior studies showing a lack of benefit following cyclophosphamide-based CM, the benefit of ICM in the modern era is unclear and we sought to determine its impact on outcomes. Considering the reasons for receiving ICM, such patients tended to harbor high-risk disease characteristics. Because of this, methods to account for the differences between those who did and did not receive ICM were required to rigorously evaluate the impact of ICM. For these purposes, we employed a propensity score matching (PSM) approach to estimate the average

treatment effect on the treated (ATT; i.e., the average treatment effect among those who received ICM). We used this approach to assess the impact of ICM on short-term complications and long-term outcomes.

METHODS

Patients

The retrospective chart review study was approved by Fred Hutchinson Cancer Center's (FHCC) Institutional Review Board based on federal regulations and the ethical standards of the FHCC Human Research Protection Program. All patients provided informed consent allowing for the collection of medical information for research. MM patients who collected autologous peripheral blood stem cells (PBSCs) with the intent to proceed directly to ASCT at FHCC between 7/2020 and 2/2023 were included for analysis. Patients were excluded if they underwent tandem autologous or sequential autologous-allogeneic hematopoietic stem cell transplantation, were undergoing salvage second ASCT, had primary PC leukemia, received non-ICM with cyclophosphamide and/or etoposide, or previously failed G ± P mobilization. All patients underwent standard pretransplant evaluation for disease burden per institutional standards prior to attempting mobilization of PBSCs.

Treatment

ICM regimens utilized are outlined in Supplementary Table 1. The most commonly used ICM regimens included VRD- (bortezomib, lenalidomide, dexamethasone) or KRD-PACE (carfilzomib, lenalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide and etoposide). Less common regimens included modified hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone); and bortezomib-hyper-CAD [11,22-24].

Per institutional practice, ICM patients also received G-CSF starting 24 to 36 hours after completion of all chemotherapy at a dose of 10 mcg/kg SC daily, and growth factor was continued through completion of leukapheresis. CD34 blood cell counts were tested on all patients when deemed appropriate and plerixafor was added before collection began if CD34 counts were low [25]. As this was a retrospective review of medical records, treatment was determined by each patient's caring attending.

Definitions

Response to treatment was categorized based on the International Myeloma Group uniform response criteria [26]. The following cytogenetic aberrations were considered high-risk chromosomal abnormalities: del(17p), t(14;16), t(4;14), t(14;20), and amp(1q). Flow cytometry was performed per institutional standards [11].

The time to neutrophil engraftment was defined as the number of days from ASCT graft infusion (day 0) until an absolute neutrophil count $\geq 0.5 \times 10^9$ cells per liter (L) for 3 consecutive days, and the time to platelet engraftment was defined as the number of days from day 0 until a platelet count of $\geq 50 \times 10^9$/L without platelet transfusion for 7 consecutive days. The total number of inpatient days was collected from day +1 through day +30. Fever was defined as a body temperature $\geq$38°C. Neutropenic fever (NF) was defined as a body temperature $\geq$38°C with an absolute neutrophil count $< 0.5 \times 10^9$/L. The presence of circulating blood PCs was defined as the detection of an abnormal PC population in the peripheral blood by flow cytometry. Standard and high-intensity maintenance therapy was defined as the receipt of a planned singlet and doublet/triplet/quadruplet, respectively, in the post-ASCT setting.

Pretransplant Evaluation

All patients underwent comprehensive disease restaging and organ function testing prior to transplant. This included (but was not necessarily limited to) a cross-sectional imaging assessment, a bone marrow evaluation (typically via bilateral biopsies), peripheral blood flow cytometry, serum protein electrophoresis with immunofixation, serum FLCs, immunoglobulin quantification, 24-hour timed urine collection with Bence Jones quantification, pulmonary function testing, dental evaluation, and a complete blood count and comprehensive metabolic panel.

All patients underwent positron emission tomography-computed tomography and/or whole-body bone marrow magnetic resonance imaging as part of their pre-ASCT evaluation. The viable disease was defined as (1) positron emission tomography-computed tomography imaging with nonphysiologic area of increased ^{18}FDG uptake (i.e., standard uptake volume max based on body weight was >2.5) with a corresponding lytic bone lesion on the CT images; or (2) bone marrow magnetic resonance imaging with focal lesions showing high signal intensity on STIR images and low signal intensity on T1-weighted images.

Supportive Care

Packed red blood cells and platelets were transfused for hematocrit <26% and platelet count

$<11 \times 10^9$/L, respectively, or where clinically indicated. Prophylactic antimicrobial therapy included acyclovir or valacyclovir, fluconazole, and levofloxacin per standard institutional guidelines. Broad-spectrum intravenous antibiotics were initiated for NF per standard institutional guidelines. In the absence of an allergy or intolerance, empiric treatment with cefepime was provided for NF. Vancomycin was added in the event of skin and soft tissue infection, clinically apparent catheter-related infection, positive blood culture with gram-positive bacteria before susceptibility results or a history of methicillin-resistant *Staphylococcus aureus*.

Statistical Analysis

Continuous variables were compared using the Wilcoxon rank sum test. Proportions were compared using Pearson's Chi-squared test or Fisher's exact test. Event-free survival (EFS) failures were defined as death, progressive disease (PD), or unplanned treatment escalation. EFS and OS were estimated via the Kaplan-Meier method. Median follow-up was estimated using the Reverse Kaplan-Meier method.

Propensity score analysis was used to estimate the effect of ICM on post-ASCT outcomes with the *MatchIt* (Version 4.5.5) package in R (Version 2023.09.0+463) [27]. Propensity scores for all patients were estimated using logistic regression, where the logit of the probability of ICM receipt was regressed on a variety of factors.

Two PSM specifications were utilized: 1:1 nearest neighbor matching and optimal full matching. The 1:1 nearest neighbor technique matches each treated individual with exactly one control individual. This is done by comparing the propensity scores of treated and control individuals and selecting the control individual with the closest distance (i.e., propensity score difference) to that of the treated individual [28,29]. Optimal full matching uses all treated and control individuals by algorithmically grouping them into a series of matched sets with the goal of achieving a balance between treated and control groups. Each matched set contains at least one treated individual and at least one control individual. If a treated individual has many control individuals with similar propensity scores, then it will be grouped with many control individuals. However, a treated individual with fewer comparable control individuals will be grouped with fewer control individuals. Optimal full matching can improve the precision of treatment effect estimates by creating more balanced matched sets compared to other matching techniques [30-32].

Weighted Cox regression was used to estimate the cause-specific hazard ratio (HR) of the event appropriate to each time-to-event outcome, weighted linear regression was used to compare continuous outcomes, and weighted logistic regression was used to compare binary outcomes. The weights for the regression models were obtained as described above. In addition, standard multivariable regression was used to compare ICM and non-CM groups.

Standard and weighted multivariable Cox regression was adjusted for mobilization (ICM versus non-CM), cytogenetic risk (standard versus high), premobilization International Myeloma Working Group (IMWG) response (at least a very good partial response [≥VGPR] versus partial response [PR] versus PD), BMPCs ≥10%, and circulating blood PCs by flow cytometry (presence versus absence). Standard and weighted multivariable linear and logistic regression were adjusted for mobilization (ICM versus non-CM), age, sex, $CD34^+$ cell dose, melphalan dose (200 versus 140 mg/m^2), cytogenetic risk (standard versus high), premobilization IMWG response (≥VGPR versus PR versus PD), BMPCs ≥10%, circulating blood PCs (presence versus absence).

RESULTS

Patient Characteristics

Of 451 patients who underwent ASCT for MM, ICM was used in 61 patients (13.5%; Supplementary Table 1). In the ICM group, IMiD/PI-PACE-based and modified hyper-CVAD regimens were given to 45 (74%) and 16 (26%), respectively. Overall, 390 patients did not receive additional salvage chemotherapy after arrival to our transplant service and only received growth factor for mobilization of autologous PBSC (non-CM group).

Induction therapy for all 451 patients involved standard quadruplet dara/IMiD/PI/dex (n = 73, 16%) and triplet PI/IMiD/dex (n = 378, 84%) treatment. For the ICM and non-CM groups, quadruplet therapy was used in 13.7% (n = 10) and 13.5% (n = 51), respectively. Notably, no patients were identified who underwent mobilization but then did not proceed to ASCT, and there were no patients in the non-CM group who had previously been treated with PACE- or modified hyper-CVAD-based induction regimens.

As expected, baseline characteristics of the patients treated with ICM and non-CM were markedly different (Table 1), with the disease features of the ICM cohort showing evidence of

Table 1
Properties of patients who received intensive chemomobilization (ICM) versus nonchemomobilization (non-CM).

Characteristic	ICM, *N* = 61	Non-CM, *N* = 390	*P* value*
BMPCs ≥10%, *n* (%)	29 (48%)	12 (3.1%)	<.001
≥VGPR, *n* (%)	23 (38%)	350 (90%)	<.001
Involved FLC (mg/dL), median (IQR)	3.8 (1.8, 17.0)	1.4 (0.9, 2.4)	<.001
M-spike (g/dL), median (IQR)	0.20 (0.00, 0.40)	0.00 (0.00, 0.10)	<.001
Circulating plasma cells, *n* (%)	13 (21%)	7 (1.8%)	<.001
High-risk cytogenetics, *n* (%)	23 (38%)	86 (22%)	.008
Melphalan 200 mg/m^2, *n* (%)	60 (98%)	354 (91%)	.045
Maintenance intensity, *n* (%)			.059
Standard	38 (69%)	297 (80%)	
None	0 (0%)	9 (2.4%)	
High	17 (31%)	67 (18%)	
Unknown	6	17	
CD34 dose x 10^6/kg, median (IQR)	5.34 (4.32, 7.56)	5.18 (4.33, 6.15)	.2
Viable disease, *n* (%)	33 (54%)	181 (46%)	.3
Induction lines, *n* (%)			.4
1	35 (57%)	253 (65%)	
2	20 (33%)	113 (29%)	
3+	6 (9.8%)	24 (6.2%)	
R-ISS 3, *n* (%)	9 (20%)	36 (17%)	.5
Unknown	17	174	
Age (years), median (IQR)	62 (55, 67)	62 (56, 68)	.6
Male sex, *n* (%)	35 (57%)	228 (58%)	.9
Quad induction, *n* (%)	10 (16%)	63 (16%)	>.9

BMPC indicates bone marrow plasma cell; VGPR, very good partial response; FLC, free light chain; R-ISS, Revised International Staging System; Viable disease, evidence of active disease on pretransplant imaging.
* Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test.

greater disease burden and adverse disease biology. A higher proportion of ICM patients had BMPCs ≥10%, circulating blood PCs, and high-risk cytogenetics; and they had greater involved FLCs and M-spikes. The number of prior lines of therapy was similar (ICM versus non-CM: median 1.0 versus 1.0, P = .2). No patients received alkylator-based therapy in the pre-ASCT setting aside from those who received it as part of their ICM regimen. Specific maintenance therapy regimens utilized, stratified by receipt of ICM and maintenance intensity, are shown in Supplementary Table 2.

Compared to non-CM patients, a higher proportion of ICM patients satisfied ≥1 indication for consideration of ICM (70% versus 7.7%, P < .001 [Pearson's Chi-squared test]; Table 1). The patient-level features of patients who received ICM therapy are shown in Figure 1. The most common features included the presence of viable disease on imaging (54.1%) and BMPCs ≥10% (47.5%). Other features included PR (39.3%) or PD (23%) to induction therapy, high-risk cytogenetics (37.7%), and circulating blood PCs (21.3%). Of note, there were two patients whose sole reason for ICM was the presence of cytogenetics abnormalities. Relevant abnormalities included del(17p) and gain (1q) in one patient, and t(14;16) and amp(1q) in the other patient.

ICM patients yielded greater CD34$^+$ cell collections (10.8 versus 10.2 × 10^6/kg, P = .018 [Wilcoxon rank sum test]) and received less plerixafor (30% versus 61%, P < .001 [Pearson's Chi-squared test]). The impact of the mobilization approach on collection yield was most pronounced among the subset of patients who did not receive plerixafor (ICM versus non-CM: 11.4 versus 10.2 × 10^6/kg, P = .008 [Pearson's Chi-squared test]).

A higher proportion of ICM patients were conditioned with high-dose melphalan at 200 mg/m^2 (98% versus 91%, P = .045 [Pearson's Chi-squared test]). The number of CD34 cells/kg infused between groups was similar. The use and intensity of post-transplant maintenance therapy between the ICM and non-CM groups was not significantly different (P = .059 [Fisher's exact test]).

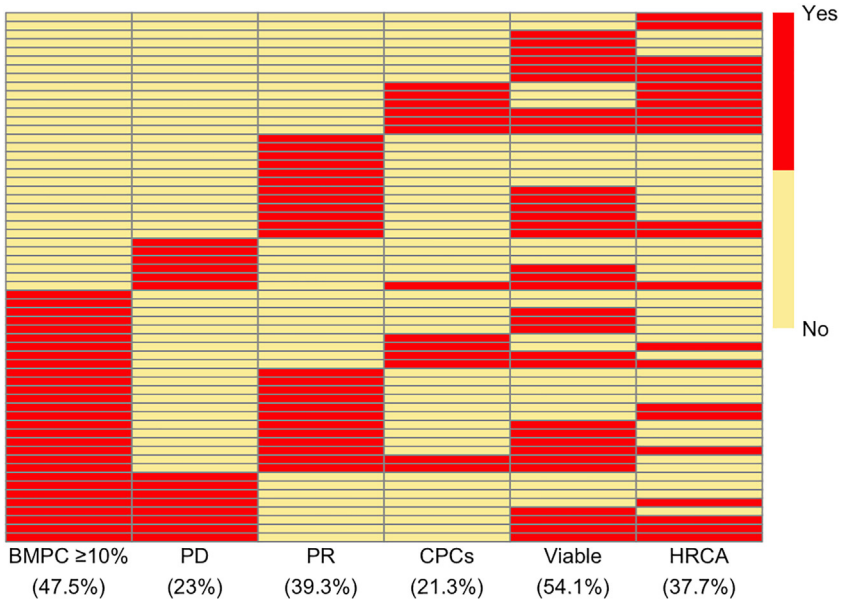

Figure 1. Features of patients who received intensive chemomobilization. Each row represents a distinct patient. BMPC, bone marrow plasma cells; PD, progressive disease; PR, partial response, CPCs, plasma cells, HRCA, high-risk chromosomal abnormality.

Response to ICM

Of the patients who underwent ICM, 51 (84%) were restaged post-ICM, among whom the overall response rate was 31% (Figure 2). However, 46 of 55 evaluable patients (84%) saw a reduction in their M-spike and/or in the difference between involved and uninvolved serum FLCs (Supplementary Figure 1a, b). Among those evaluated with peripheral blood flow cytometry pre- and post-ICM (n = 8), 5 patients (63%) cleared their circulating blood PCs. Among those who underwent a repeat bone marrow biopsy post-ICM, a BMPC reduction was seen in 17 of 22 patients (77%; Supplementary Figure 1c), and there was a significant decrease in the median BMPCs (pre versus post: 20% versus 7.8%, P = .002; note: if a BMPC range was provided, the average value was utilized).

Toxicity Following ICM

Eleven patients (18%) required post-ICM/pre-ASCT hospitalization due to NF without a source (n = 5), infection (n = 4), severe hypertension (n = 1; following KRD-PACE), and new-onset atrial fibrillation with rapid ventricular response (n = 1; following VRD-PACE).

PSM

In a multivariable logistic regression model for receipt of ICM, the following factors were included: BMPCs ≥10% (binary), presence of circulating blood PCs (binary), involved FLC (mg/dL; continuous), and M-spike (g/dL; continuous), cytogenetic risk (standard versus high; binary), sex (male versus female; binary), presence of viable disease (binary) and age (years; continuous;

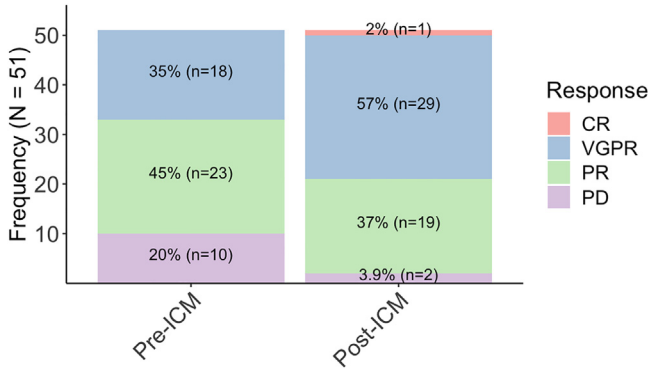

Figure 2. Impact of intensive chemomobilization on disease status. IMWG responses pre- and post-chemomobilization among patients evaluable at both time points.

Supplementary Figure 2a, b). The following factors, which were found to be independently associated with receipt of ICM, were included as covariates in our PSM model: BMPCs ≥10%, presence of circulating blood PCs, involved FLC, and M-spike. Of note, BMPCs were dichotomized as <10% versus ≥10% because this threshold was the most common primary reason for the provision of ICM and it additionally reflects a major component of the IMWG diagnostic criteria for MM [33].

We first attempted 1:1 nearest neighbor PSM without replacement with a propensity score estimated using logistic regression of the treatment on the covariates. This matching specification yielded a relatively poor balance. We next performed optimal full matching using the propensity scores, which use all treated and all control units without discarding any units through matching, to achieve a balance between ICM and non-CM groups. To depict the balance of the covariates from which the propensity scores are derived, a Love plot of absolute standardized mean differences is shown in Supplementary Figure 2c.

To achieve adequate balance, the absolute standardized mean differences should be less than 0.25, and the ratio of variances of the propensity score in the treated and control groups should be between 0.5 and 2 [34]. After balancing the covariates using optimal full matching, the absolute standardized mean differences were <0.25 with the exception of BMPCs ≥10%, which was 0.28, suggesting an adequate balance of most covariates, with the suboptimal balance of BMPCs ≥10%. The variance ratios of the continuous variables were 0.87 for M-spike and 60 for involved FLC, suggesting good balance for M-spike and suboptimal balance for involved FLC.

For clarity, all subsequent usage of the term "PSM" will reflect optimal full matching. The distribution of weights assigned to the control units for each matched set created by PSM is shown in Supplementary Figure 2d. The distribution of propensity scores with the respective weights assigned through PSM is shown in Supplementary Figure 2e. A comparison of characteristics of ICM and PSM-weighted non-CM cohorts is shown in Supplementary Table 3. All assessed characteristics were comparable between the groups except for the proportion of patients who received melphalan 200 mg/m^2 (ICM versus non-CM: 98% versus 89%, P = .042 [Chi-squared test with Rao and Scott's second-order correction]).

Transplant Toxicity

The following post-ASCT metrics were evaluated: inpatient duration, days to neutrophil and platelet engraftment, receipt and number of doses of cefepime and vancomycin, number of febrile days, NF, and incidence of bacteremia.

A comprehensive list of regression output is provided in Supplementary Table 4. Notably, in multivariable PSM analysis, ICM was associated post-ASCT with longer inpatient duration (+4.1 days, 95% CI, 2.4 to 5.8, P < .001), more febrile days (+0.96 days, 95% CI 0.50 to 1.4, P < .001), impaired time to platelet engraftment (HR 0.23, 95% CI 0.06 to 0.87, P = .031), greater incidence of bacteremia (OR 3.41, 95% CI 1.20 to 9.31, P = .018), and increased antibiotic usage (cefepime: +2.3 doses, 95% CI 0.39 to 4.1, P = .018; vancomycin: +1.0 doses, 95% CI 0.23 to 1.8, P = .012). No patients in the ICM cohort failed to engraft neutrophils or platelets. A single patient in the non-CM cohort did not achieve engraftment at the time of discharge from the transplant service. After excluding this patient from analysis using a PSM-weighted multivariable linear regression model, the average time to platelet engraftment was longer in the ICM cohort by 1.7 days (95% CI 9.86 to 2.6, P < .001).

EFS and OS Post-ASCT

Pre-PSM, the median post-ASCT follow-up of the whole cohort was 30.6 months, and among the ICM and non-CM subsets was 34.8 months and 29.8 months, respectively. Post-PSM, the median post-ASCT follow-up of the whole cohort was 29.8 months, and among the PSM-weighted non-CM subset was 31.1 months.

The median EFS in the ICM and PSM-weighted non-CM cohorts was 34.0 and 12.4 months, respectively (Figure 3). A description of the events comprising the EFS endpoint is shown in Supplementary Table 5. Median OS was not reached in the ICM and PSM-weighted non-CM cohorts.

Unsurprisingly, ICM was not demonstrably associated with superior OS and EFS in non-PSM univariate and multivariable analyses (Supplementary Figure 3). In PSM multivariable analysis (Figure 4), ICM was associated with improved EFS (HR 0.30, 95% CI 0.14 to 0.67, P = .003), but not with improved OS (HR 0.38, 95% CI 0.10 to 1.44, P = .2).

Sensitivity Analyses

To gauge the robustness of the effect of ICM on EFS, we conducted several sensitivity analyses (Supplementary Table 6).

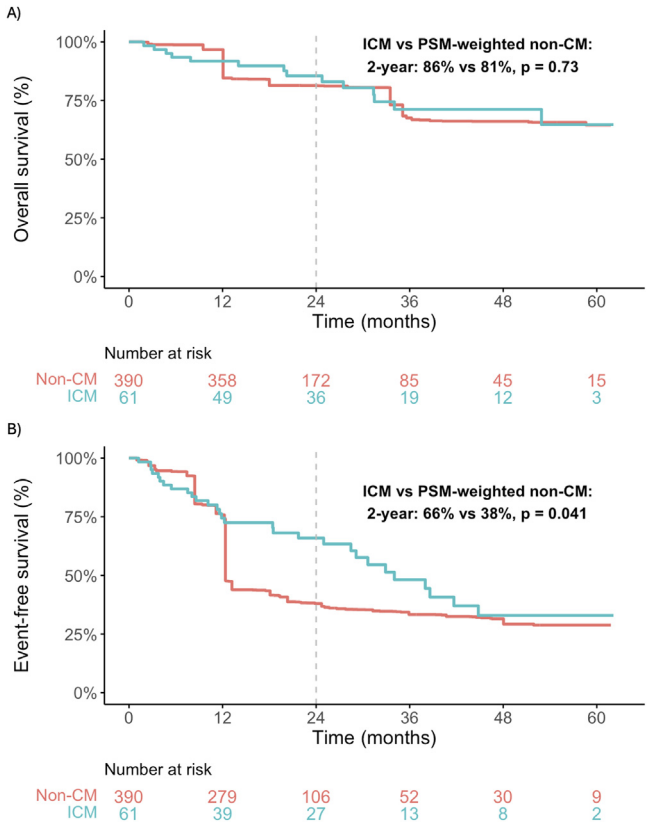

Figure 3. PSM-weighted Kaplan-Meier estimates of (A) overall survival and (B) event-free survival. Blue = intensive chemomobilization (ICM); red = PSM-weighted nonchemomobilization (CM). 2-year point estimates were compared using a *z*-test.

Sensitivity analysis #1: Exclusion of patients with PD

Exclusion of patients with PD found during pre-ASCT evaluation yielded 435 total patients (ICM, $n = 47$; non-CM, $n = 388$). In the PSM multivariable analysis of this subset, ICM was associated with improved EFS (HR 0.24, 95% CI 0.09 to 0.65, $P = .005$).

Sensitivity analysis #2: Incorporation of response status and cytogenetic risk level into the propensity score model

IMWG response (≥VGPR versus PR/PD) and cytogenetic risk level (high versus normal) were incorporated into the propensity score model. After matching the covariates, the absolute standardized mean differences were <0.25 for all covariates. The variance ratios of the continuous variables were 1.86 for M-spike and 101 for involved FLC, suggesting good balance for M-spike and suboptimal balance for involved FLC. ICM was associated with EFS in PSM univariate (HR 0.53, 95% CI 0.32 to 0.85, $P = .009$) and PSM multivariable (HR 0.25, 95% CI 0.12 to 0.53, $P < .001$) models.

Sensitivity analysis #3: Exclusion of patients with propensity scores outside the range of the alternate treatment group

The maximum propensity score (PS_{max}) in the non-CM group and the minimum propensity score (PS_{min}) in the ICM group were 0.896 and 0.027, respectively. Excluding patients outside this PS_{min} to PS_{max} range yielded 413 total patients (ICM, $n = 46$; non-CM, $n = 367$). In the PSM multivariable analysis of this subset, ICM was associated with improved EFS (HR 0.27, 95% CI 0.11 to 0.66, $P = .004$).

Sensitivity analysis #4: Modifications to treatment of BMPC enumeration

a) *Treatment of BMPC percentage as a continuous variable*

BMPC percentages were treated as a continuous variable in the propensity score and multivariable regression models. Where a range was described in the pathology report, the average value was used. After matching the covariates, the absolute standardized mean differences were <0.25 for all covariates. The variance

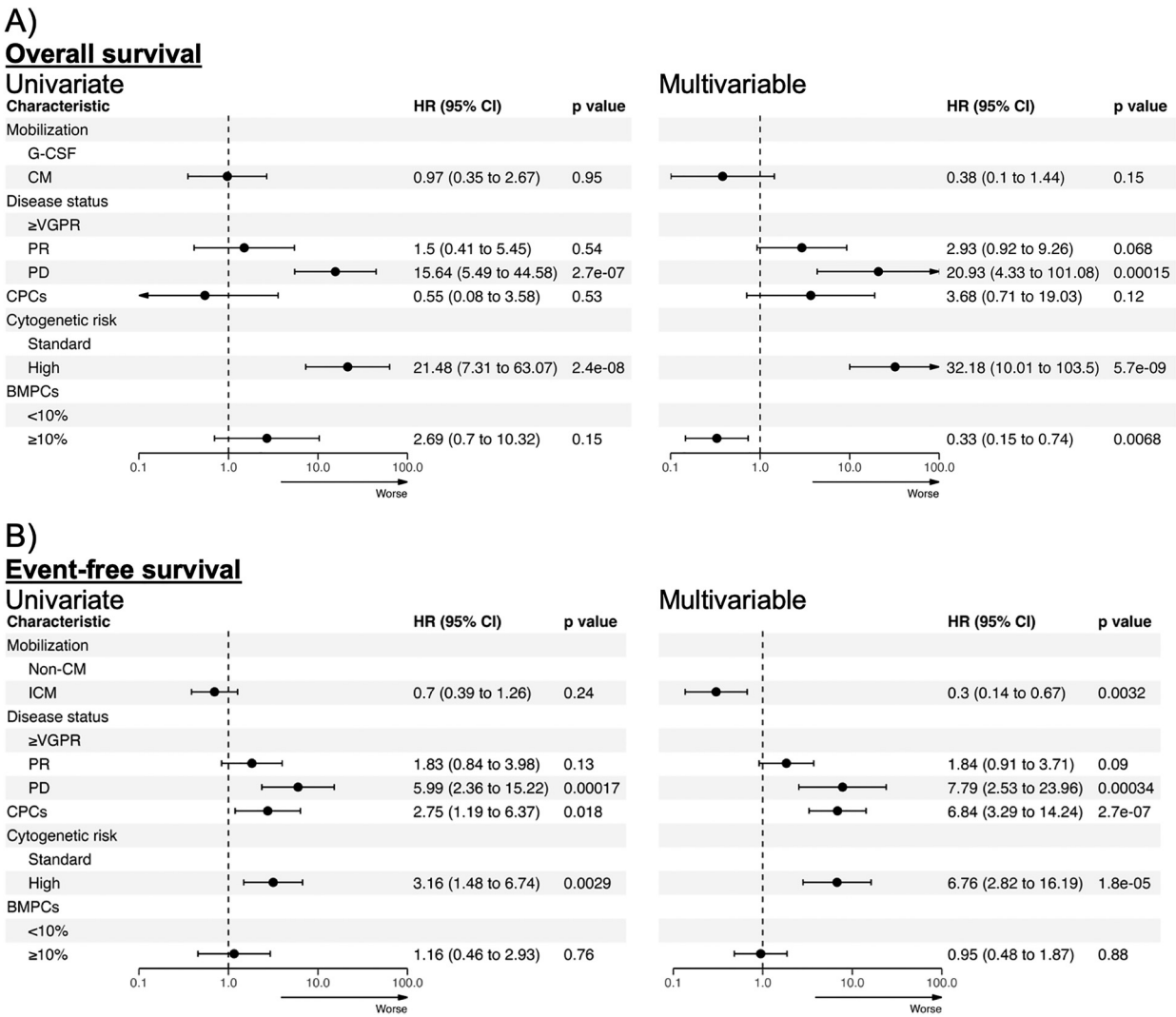

Figure 4. Propensity score matching Cox regression analysis for (A) overall survival and (B) event-free survival. CM, intensive chemomobilization; VGPR, very good partial response; PR, partial response; PD, progressive disease; CPCs, circulating plasma cells; BMPCs, bone marrow plasma cells.

ratios of the continuous variables were 2.0 for M-spike, 97.5 for involved FLC, and 5.9 for BMPC percentage. This suggests good balance for M-spike, and suboptimal balance for involved FLC and BMPC percentage. In PSM multivariable analysis, ICM was associated with improved EFS (HR 0.36, 95% CI 0.18 to 0.74, $P = .005$).

b) *Utilization of a BMPC threshold of ≥5%*

BMPC percentage was treated as a binary variable using a threshold of ≥5% versus <5% in propensity score and regression models. The variance ratios of the continuous variables were 1.8 for M-spike and 92 for involved FLC. This suggests good balance for M-spike, and suboptimal balance for involved FLC. In PSM multivariable analysis, ICM was associated with improved EFS (HR 0.34, 95% CI 0.15 to 0.73, $P = .006$).

DISCUSSION

In our analysis of 451 newly diagnosed MM patients who underwent autologous PBSC collection before planned ASCT, ICM was administered to 14% of patients, all of whom proceeded to ASCT. ICM was reserved for patients felt to have excessive residual disease burden at pre-ASCT workup, predominantly the presence of BMPCs ≥10%. Among evaluable patients, ICM deepened IMWG responses in 31% and cleared circulating blood PCs in 63%. Re-admission attributable to toxicity of CM occurred in 18%, typically for NF or infectious complications. These results are similar to the re-admission frequencies previously reported following KRD-PACE (26%) and VD-PACE (24%) [9,11].

Since the patients who received ICM had relatively adverse MM disease characteristics, ICM would not have been realistically offered to most

patients in the non-CM cohort. To appropriately evaluate the impact of ICM among those who potentially could have received it and did not get it, we utilized a PSM approach that estimated the ATT (i.e., the average treatment effect among those who received ICM).

In PSM analysis, the use of ICM impacted post-ASCT outcomes. Most notably, ICM was associated with significantly improved EFS after adjustment for various factors. The estimated median EFS was increased by 2.8-fold. In the immediate post-ASCT setting, however, ICM was associated with increased inpatient duration, more febrile days, greater antibiotic usage, greater incidence of bacteremia, and delayed platelet engraftment. To our knowledge, we are the first to provide evidence that ICM may improve long-term outcomes in selected MM patients.

Limited research has been conducted to assess the efficacy of ICM on long-term ASCT outcomes. A recent retrospective study by Vaxman et al. explored outcomes related to CM, encompassing patients treated with ICM (i.e., VD-PACE). Although a matching approach was implemented, relatively poor OS and progression-free survival were not overcome with CM in this analysis. There are several key reasons why this study did not detect a benefit for CM and reached a different conclusion than our study for ICM: (1) only a minority within the CM cohort received intensive regimens (n = 21, 18%), whereas the majority (n = 96, 82%) received cyclophosphamide alone; (2) the predominant rationale for CM was overt relapse rather than responding to standard therapy but still having excessive disease burden; and (3) the matched control cohort reflected a less aggressive patient population than those who received CM [9]. In this regard, the major strengths of our study include a relatively large cohort of patients who received ICM, utilization of ICM for cytoreduction outside of overt relapse, and achievement of superior matching between our ICM and non-CM control groups.

The major limitation of our study lies in the challenge of dealing with dramatic differences in patient and disease characteristics between ICM and non-CM cohorts in the setting of a large imbalance in the number of patients in each group (~6:1 ratio of non-CM to CM). We attempted to mitigate these differences using a PSM approach. However, some individuals who received ICM exhibited outlier characteristics in terms of the aggressiveness of measured disease parameters, creating an unaccounted-for imbalance in disease profiles whereby the ICM patients had more aggressive disease features than the PSM-weighted non-CM control group. This imbalance may have led to relatively favorable outcomes in our PSM-weighted non-CM group, thus diminishing the observed benefit of ICM in our study. Furthermore, PSM analysis assumes that all confounding variables affecting both treatment assignment and outcome are measured and included in the propensity score model. However, it is difficult to identify and measure all relevant confounders. Failing to account for unmeasured confounders can lead to biased estimates of treatment effects. Ultimately, only a randomized trial will have sufficient rigor to answer the question of whether ICM is beneficial for selected high-risk MM patients, and whether certain subpopulations derive greater benefit.

CONCLUSION

Among patients with excessive MM disease burden uncovered during pre-ASCT evaluation, ICM was independently associated with improved EFS in a multivariable PSM analysis. This came at the cost of regimen-related toxicities, often requiring re-admission, as well as more post-ASCT issues including longer inpatient stays, increased antibiotic usage, greater incidence of bacteremia, and more febrile days in the immediate post-ASCT setting. Prospective studies are needed to validate these findings and better identify patients for whom the benefits of ICM outweigh the risks.

AUTHOR CONTRIBUTIONS

AJP interpreted data and drafted the manuscript. AJC conceived the study, interpreted data, edited the manuscript, and provided critical oversight. ACY, RB, LH, NW, DJG, MM, AKG, TG, PS reviewed and edited the manuscript. TG and PS provided statistical support and data analysis.

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Conflict of Interest Statement: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2024.05.016.

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