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Autologous

Revised International Staging System Is Predictive and Prognostic for Early Relapse (<24 months) after Autologous Transplantation for Newly Diagnosed Multiple Myeloma

Sathish Gopalakrishnan[1], Anita D'Souza[2], Emma Scott[3], Raphael Fraser[2,4], Omar Davila[2], Nina Shah[5], Robert Peter Gale[6], Rammurti Kamble[7], Miguel Angel Diaz[8], Hillard M. Lazarus[9], Bipin N. Savani[10], Gerhard C. Hildebrandt[11], Melhem Solh[12], Cesar O. Freytes[13], Cindy Lee[14], Robert A Kyle[15], Saad Z. Usmani[16], Siddhartha Ganguly[17], Amer Assal[18], Jesus Berdeja[19], Abraham S. Kanate[20], Binod Dhakal[21], Kenneth Meehan[22], Tamila Kindwall-Keller[23], Ayman Saad[24], Frederick Locke[25], Sachiko Seo[26], Taiga Nishihori[25], Usama Gergis[27], Cristina Gasparetto[28], Tomer Mark[29], Yago Nieto[30], Shaji Kumar[15], Parameswaran Hari[2,*]

[1] *Health Science North, Sudbury, Ontario, Canada*
[2] *CIBMTR (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Center for Hematologic Malignancies, The Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon*
[4] *Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin*
[5] *Department of Stem Cell Transplantation, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[6] *Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom*
[7] *Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas*
[8] *Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain*
[9] *Seidman Cancer Center, Division of Hematology Oncology, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, Ohio*
[10] *Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee*
[11] *Markey Cancer Center, University of Kentucky, Lexington, Kentucky*
[12] *The Blood and Marrow Transplant Group of Georgia, Northside Hospital, Atlanta, Georgia*
[13] *Texas Transplant Institute, San Antonio, Texas*
[14] *Royal Adelaide Hospital, Adelaide, SA, Australia*
[15] *Mayo Clinic Rochester, Rochester, Minnesota*
[16] *Department of Hematologic Oncology & Blood Disorders, Levine Cancer Institute/Atrium Health, Charlotte, North Carolina*
[17] *Division of Hematological Malignancy and Cellular Therapeutics, University of Kansas Health System, Kansas City, Kansas*
[18] *Columbia University Medical Center, New York, New York*
[19] *Sarah Cannon BMT Program, Nashville, Tennessee*
[20] *Osborn Hematopoietic Malignancy and Transplantation Program, West Virginia University, Morgantown, West Virginia*
[21] *Medical College of Wisconsin, Division of Hematology Oncology; Milwaukee, Wisconsin*
[22] *Dartmouth Hitchcock Medical Center, Lebanon, New Hampshire*
[23] *Division of Hematology/Oncology, University of Virginia Health System, Charlottesville, Virginia*
[24] *Division of Hematology/Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama*
[25] *Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida*
[26] *Department of Hematology & Oncology, National Cancer Research Center East, Chiba, Japan*
[27] *Hematolgic Malignancies & Bone Marrow Transplant, Department of Medical Oncology, New York Presbyterian Hospital/Weill Cornell Medical Center, New York, New York*
[28] *Duke University Medical Center, Durham, North Carolina*
[29] *University of Colorado Hospital, Division of Hematology Oncology; Aurora, Colorado*
[30] *Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas M.D. Anderson Cancer Center, Houston, Texas*

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A B S T R A C T

The revised International Staging System (R-ISS) combines ISS with genetic markers and lactate dehydrogenase and can prognosticate newly diagnosed multiple myeloma (MM). Early relapse (<24 months) after upfront autologous hematopoietic cell transplantation (AHCT) strongly predicts inferior overall survival (OS). We examined the ability of R-ISS in predicting early relapse and its independent prognostic effect on postrelapse survival after an

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* Correspondence and reprint requests: Parameswaran Hari, MD, MS, CIBMTR, Department of Medicine, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.
E-mail address: phari@mcw.edu (P. Hari).

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early relapse. Using the Center for International Blood and Marrow Transplant Research database we identified MM patients receiving first AHCT within 18 months after diagnosis with available R-ISS stage at diagnosis (n = 628). Relative risks of relapse/progression, progression-free survival (PFS), and OS were calculated with the R-ISS group as a predictor in multivariate analysis. Among early relapsers, postrelapse survival was tested to identify factors affecting postrelapse OS. The cumulative incidence of early relapse was 23%, 39%, and 50% for R-ISS I, R-ISS II, and R-ISS III, respectively ($P < .001$). Shorter PFS and OS were seen with higher stage R-ISS. R-ISS was independently predictive for inferior postrelapse OS among early relapsers, as was the presence of ≥3 comorbidities and the use of ≥2 induction chemotherapy lines. R-ISS stage at diagnosis predicts early post-AHCT relapse and independently affects postrelapse survival among early relapsers.

INTRODUCTION

Novel antimyeloma agents, including proteasome inhibitors and immunomodulatory drugs, incorporated into induction therapy before high-dose therapy and autologous hematopoietic cell transplant (AHCT) have significantly improved survival in multiple myeloma (MM) patients over the past 2 decades, as shown by randomized trials and retrospective series [1,2]. Nonetheless, responses to novel agents vary among various biologic subgroups [3]. A clearer understanding of the important prognostic factors for survival can improve risk stratification and therapeutic decision-making.

Available evidence shows a strong association between pretransplant depth of response and post-transplant progression-free survival (PFS) and overall survival (OS) [4,5]. Despite achieving deep pre-AHCT responses, some patients relapse early and have very poor OS [6,7]. Similarly, data from the Arkansas group suggest that the loss of an established complete response in the first 3 years confers an inferior prognosis when compared with a lower level of response that is sustained over time [8]. Thus, early relapse represents a dynamic high-risk marker that is unknown at diagnosis and available only during the natural course of disease evolution.

The revised International Staging System (R-ISS), proposed in 2015 as a more accurate prognostic model for newly diagnosed MM, incorporates ISS stage, serum lactate dehydrogenase, and high-risk cytogenetics assessed by interphase fluorescent in situ hybridization. High-risk cytogenetic abnormalities defined as the presence of del(17p) and/or t(4;14) and/or t(14;16) or an elevated lactate dehydrogenase above the upper limit of normal are risk factors that upstage patients in the R-ISS system. At a median follow-up of 46 months, the 5-year OS rate was 82% in the R-ISS I, 62% in the R-ISS II, and 40% in the R-ISS III groups; the 5-year PFS rates were 55%, 36%, and 24%, respectively [9]. We analyzed the impact of R-ISS stage at diagnosis to predict early post-AHCT relapse (defined as relapse/progression within 24 months after AHCT) and the influence of the R-ISS stage on postrelapse survival using the Center for International Blood and Marrow Transplant Research (CIBMTR) database.

METHODS

Data Sources

The CIBMTR is research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. It comprises a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on allogeneic and AHCT. Participating centers are required to report all transplants consecutively; compliance is monitored by onsite audits, and patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and onsite audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

The CIBMTR collects data at 2 levels: Transplant Essential Data (TED) level and Comprehensive Report Form (CRF) level. The TED-level data are an internationally accepted standard data set that contains a limited number of key variables for all consecutive transplant recipients. TED-level data, with some additional details of donor and graft characteristics, comprise the obligatory data submitted to the Stem Cell Therapeutic Outcomes Database. When a transplant is registered with the CIBMTR, a subset of patients are selected for the CRF level of data collection through a weighted randomization scheme. The CRF level captures additional patient-, disease-, and treatment-related data. TED- and CRF–level data are collected pretransplant, 100 days and 6 months post-transplant, annually until year 6 post-transplant, and biannually thereafter until death.

Patient Selection

Patients with MM receiving an upfront AHCT, defined as AHCT within 18 months after diagnosis, with melphalan conditioning after a novel agent-based induction and transplanted between 2008 and 2014 were included in this analysis. Based on the availability of all components of the R-ISS schema, 628 patients were included. The same data set was used for a recently published CIBMTR analysis [10].

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study population using the median value and range for continuous variables and the frequency and percentage for categorical variables. Group comparisons were done by the Kruskall-Wallis test, chi-square test, and Fisher exact test. The endpoints of interest included disease response, PFS, and OS after transplant. Transplant-related mortality was defined as mortality after transplant in the absence of disease relapse or progression. Disease response and progression were assessed using the International Myeloma Working Group consensus criteria [11]. PFS was defined as the interval without progressive disease with patients alive and without progression/relapse censored at last follow-up. OS was defined as time interval from diagnosis or time of relapse (in the case of postrelapse OS) until death from any cause with survivors censored at last follow-up. Survival probabilities were calculated by using the Kaplan-Meier estimator with the variance estimated by Greenwood's formula. We also examined postrelapse survival from the date of relapse/progression in patients with documented relapse or myeloma progression occurring within 24 months of AHCT. Age, gender, Karnofsky score, R-ISS, HCT-specific comorbidity index (HCT-CI), clinical trial enrollment, novel versus nonnovel induction treatment, lines of chemotherapy, disease status at transplant, time from diagnosis to transplant, year of transplant, and melphalan conditioning dose were tested in multivariate analysis.

RESULTS

Patient characteristics and treatment details are shown in Table 1. More patients in the R-ISS III cohort required more than 1 line of chemotherapy before AHCT (29% compared with 20% for R-ISS II and 15% for R-ISS I). Eighty–seven percent of patients proceeded to AHCT within 12 months of diagnosis. Pretransplant disease status of at least very good partial response was similar across R-ISS stages I, II, and III at 49%, 53%, and 52%, respectively. Post-transplant maintenance was administered to 74%, 68%, and 70%, respectively, within each R-ISS stage cohort.

Univariate Analysis for Relapse/Progression, PFS, and OS

The incidence of relapse/progression was higher and PFS/OS inferior with higher R-ISS stage (Table 2). The cumulative incidence of early relapse within 24 months of AHCT was 23% for R-ISS I, 39% for R-ISS II, and 50% for R-ISS III groups ($P < .001$). Table 2 summarizes the survival data. Three-year PFS for R-ISS stages I, II, and III were 64% (57% to 71%), 47% (41% to 53%), and 32% (20% to 45%; $P < .001$) respectively. The 3-year OS for R-ISS

Table 1
Characteristics of US Adult Patients Who Underwent Melphalan Based First Autologous Peripheral Blood MM Transplant from 2008 to 2014 and Reported with CIBMTR

	R-ISS I Group (n = 199)	R-ISS II Group (n = 360)	R-ISS III Group (n = 69)
Number of centers	55	64	33
Median age at HCT, yr (range)	59 (41-76)	60 (40-78)	60 (43-75)
Male gender	115 (58)	213 (59)	41 (59)
Karnofsky score			
90-100	120 (60)	198 (55)	35 (51)
< 90	73 (37)	156 (43)	29 (42)
Missing	6 (3)	6 (2)	5 (7)
HCT-CI score			
0	85 (43)	108 (30)	15 (22)
1	28 (14)	61 (17)	9 (13)
2	26 (13)	66 (18)	15 (22)
≥3	60 (30)	122 (33)	30 (43)
Missing	0	3 (<1)	0
Clinical trial enrollment	76 (38)	118 (33)	18 (26)
Lactate dehydrogenase at diagnosis ≥ upper limit	0	71 (20)	58 (84)
ISS stage at diagnosis			
Stage I	199	45 (13)	0
Stage II	0	214 (59)	0
Stage III	0	101 (28)	69
Cytogenetic abnormality (conventional or fluorescent in situ hybridization)			
t(4;14) only	0	16 (4)	8 (12)
t(14;16) only	0	4 (1)	3 (4)
Del17p only	0	14 (4)	4 (6)
1q abnormality	13 (7)	25 (7)	5 (7)
≥2 high risk	0	9 (3)	5 (7)
No high-risk abnormality	186 (93)	292 (81)	44 (64)
Lines of chemotherapy			
1	170 (85)	289 (80)	49 (71)
≥2	29 (15)	71 (20)	20 (29)
Pretransplant induction chemotherapy			
VTD	15 (8)	18 (5)	5 (7)
VRD	89 (45)	162 (45)	31 (45)
VCD	29 (15)	59 (16)	15 (22)
VD	17 (9)	37 (10)	9 (13)
RD	35 (18)	68 (19)	5 (7)
TD	14 (7)	16 (4)	4 (6)
Disease status before HCT			
sCR/CR	41 (21)	70 (19)	12 (17)
VGPR	55 (28)	122 (34)	24 (35)
PR/SD/PD	103 (52)	168 (47)	11 (48)
Melphalan dose, mg/m^2			
140	46 (23)	89 (25)	19 (28)
200	153 (77)	271 (75)	50 (72)
Time from diagnosis to transplant			
≤6 mo	69 (35)	139 (39)	31 (45)
6-12 mo	110 (55)	172 (48)	29 (42)
12-18 mo	20 (10)	49 (14)	9 (13)
Year of transplant			
2008	44 (22)	94 (26)	11 (16)
2009	17 (9)	32 (9)	6 (9)
2010	8 (4)	23 (6)	10 (14)
2011	30 (15)	46 (13)	6 (9)
2012	39 (20)	46 (13)	8 (12)
2013	30 (15)	70 (19)	9 (13)
2014	31 (16)	49 (14)	19 (28)
Planned post-transplant treatment	147 (74)	245 (68)	48 (70)
Median follow-up of survivors, mo (range)	47 (6-97)	48 (3-99)	40 (12-97)

Values are n (%) unless otherwise defined. V indicates bortezomib; T, thalidomide; D, dexamethasone; R, lenalidomide; C, cyclophosphamide; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease.

stages I, II, and III were 88% (95% confidence interval, 83 to 93), 75% (95% confidence interval, 70 to 80), and 56% (95% confidence interval, 43 to 69; $P < .001$), respectively.

Multivariate Analysis for OS and Postrelapse Survival for Early Relapses

Multivariate analysis showed that R-ISS stage III at diagnosis was independently prognostic for both OS from transplant (Table 3) and postrelapse survival in early relapses (Table 4). Higher R-ISS stage, HCT-CI ≥ 3, ≥2 lines of pre-ASCT chemotherapy, and relapse after full–dose melphalan conditioning with 200 mg/m^2 were significant factors associated with shorter OS overall. Although treatment era (2008 to 2011 versus 2012 to 2014) was a significant prognostic factor for OS in the entire cohort, it was not significant for survival in the early relapse cohort. Figure 1 shows postrelapse survival by R-ISS groups. Median postrelapse survival after an early relapse was 4.1 years, 2.5 years, and 1.5 years for R-ISS stage I, stage II, and stage III at diagnosis, respectively.

Table 2
Univariate Analysis of R-ISS Stage

	Stage I (n = 199)		Stage II (n = 360)		Stage III (n = 69)		
Outcomes	No. Assessable	Probability (95% CI)	No. Assessable	Probability (95% CI)	No. Assessable	Probability (95% CI)	*P*
Relapse/progression	198		358		69		<.001
1 yr		10 (6-14)		21 (17-26)		38 (27-49)	<.001
2 yr		23 (17-29)		39 (33-44)		50 (38-62)	<.001
3 yr		35 (28-42)		50 (44-55)		65 (51-78)	<.001
PFS	198		358		69		<.001
1 yr		90 (85-94)		77 (72-81)		61 (49-72)	<.001
2 yr		77 (70-82)		59 (54-64)		47 (35-59)	<.001
3 yr		64 (57-71)		47 (41-53)		32 (20-45)	<.001
OS	199		360		69		<.001
1 yr		97 (95-99)		93 (90-95)		88 (80-95)	.005
2 yr		96 (92-98)		85 (81-88)		71 (59-82)	<.001
3 yr		88 (83-93)		75 (70-80)		56 (43-69)	<.001

Values are percents. CI indicates confidence interval.

Table 3
Multivariate Analysis for OS for the Entire Cohort (R-ISS)

Parameter	Level	No. of Cases		Hazard Ratio	95% Hazard Ratio Confidence Limits		*P*
		606					
R-ISS			Overall				.0004
	I	193		1.00			
	II	349		1.83	1.225	2.726	.003
	III	64		2.82	1.657	4.813	.0001
HCT-CI			Overall				.013
	0	204		1.00			
	1-2	199		1.02	.687	1.526	.907
	3+	203		1.66	1.129	2.444	.010
Lines of chemotherapy			Overall				.007
	1	491		1.00			
	2+	115		1.65	1.14	2.30	.007
Year of transplant			Overall				.006
	2012-2014	296		1.00			
	2008-2011	310		1.77	1.179	2.652	.006

Table 4
Multivariate Analysis of OS in Patients Who Relapse Early

Parameter	Level	No. of Cases		Hazard Ratio	95% Hazard Ratio Confidence Limits		*P*
		197					
R-ISS			Overall				.036
	I	42		1.00			
	II	126		1.31	.824	2.089	.252
	III	29		2.15	1.190	3.879	.011
HCT-CI			Overall				.017
	0	65		1.000			
	1-2	61		.95	.593	1.520	.827
	3+	71		1.69	1.091	2.624	.019
Lines of chemotherapy			Overall				.037
	1	146		1.00			
	2+	51		1.52	1.026	2.252	.037
Melphalan dose			Overall				.023
	140	54		1.00			
	200	143		1.65	1.072	2.537	.023

Analysis is limited to patients relapsing <24 months post-transplant).

Impact of Maintenance therapy

Intent to post-transplant maintenance therapy was reported in 74%, 68%, and 70% of R-ISS I, II, and III patients, respectively (Table 1). Comparison of survival after early relapse between those who received maintenance and those who did not (Table 5) indicated no difference in survival after early relapse regardless of utilization of maintenance post–AHCT (P = .86). The median time to relapse post-transplant was similar in the maintenance and no maintenance arms. Because our analysis was specifically looking at impact of maintenance in postrelapse OS, this study does not report on response or rate of relapse in the maintenance versus no maintenance cohorts. Likewise, because all maintenance strategies were taken together, impact of proteasome inhibitors versus immunomodulatory agents in maintenance is not included in this analysis.

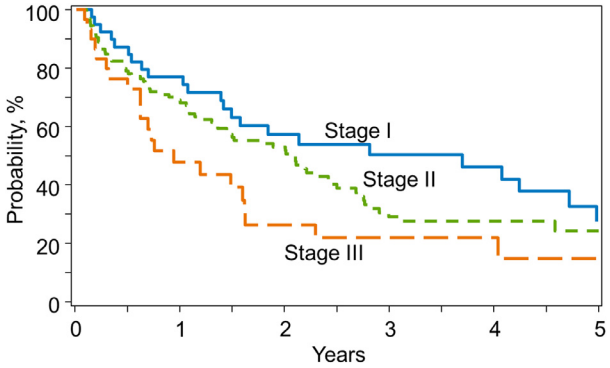

Figure 1. Postrelapse survival of early relapsers by R-ISS.

DISCUSSION

In this contemporaneous CIBMTR study, we make the following clinically important observations: (1) R-ISS stage predicts for early relapse after an upfront AHCT; (2) R-ISS independently predicts for postrelapse survival among those relapsing early; (3) in addition to R-ISS, higher HCT-CI, number of lines of induction chemotherapy pre-AHCT, and relapse after standard–dose melphalan when compared with lower dose of melphalan were associated with inferior postrelapse survival among early relapse patients; and (4) maintenance treatment did not impact postrelapse survival among early relapsers.

Early relapse defined as relapse within 24 months after AHCT for newly diagnosed MM remains an area of therapeutic challenge even in the modern era of myeloma. Although high–risk cytogenetics and depth of response post–AHCT have been identified as high risk for early relapse [12], these factors alone have not been able to characterize the group of patients who have high-risk MM. We and others have shown that early relapse post-AHCT is an important prognostic factor determining survival [6,12]. In this current analysis, we found that despite achievement of deep responses pre-AHCT (approximately 50% of patients achieve at least very good partial response status pre-AHCT), a significant proportion of patients in all R-ISS stages (23% stage I; 39% stage II; 50% stage III) relapse in under 24 months. A recent CIBMTR analysis studying early relapse during 3 different time periods found that the incidence of early relapse remained unchanged at ~35% between 2001 to 2004, 2005 to 2008, and 2009 to 2013 [13] in spite of more patients receiving planned maintenance (72% compared with 6%) between the 2009 to 2013 and 2001 to 2004 periods. The apparent constancy in the incidence of early relapse despite widespread adoption of novel agents and early AHCT is consistent with the notion that most benefit from novel agents for MM has accrued to biologically standard–risk patients [14–16]. This also means that our current armamentarium for frontline management of myeloma does not address the innate biologic features that contribute toward early relapse. Prospective trials of monoclonal antibodies such as daratumumab or elotuzumab added to triplet regimens are ongoing, and it remains to be seen whether they can reduce the incidence of early relapse [17].

In addition to R-ISS, HCT-CI > 2, receipt of >1 line of pre-AHCT chemotherapy, and year of AHCT 2008 to 2011 (compared with 2012 to 2014) were associated with worse OS in this cohort. HCT-CI and lines of treatment have been shown to be associated with OS in MM in multiple studies [18-20]. Similarly, receipt of more than 1 line of therapy before AHCT has not shown to be of benefit even among patients who achieve suboptimal response to first line of treatment [21]. Year of transplant is a close surrogate for use of maintenance therapy during this period [21,22]. Indeed, in our study 29% of patients were reported to receive maintenance therapy in 2008 to 2011 compared with 51% in 2012 to 2014.

Survival after early relapse is poor despite availability of novel agents. The median OS of R-ISS I, II, and III are 4.1, 2.5, and 1.5 years, respectively, in our analysis. R-ISS III at diagnosis was an independent prognostic factor even at the time of early relapse. Kumar et al. [6] reported that in myeloma patients treated between 1994 and 2006, relapse within a year after AHCT confers poor prognosis, with a median OS of 10.8 months from the time of relapse. In our recent CIBMTR analysis, the median postrelapse survival after early relapse was 24 months for those transplanted after 2005 compared with 16 months for those transplanted before 2005 [13]. Although there was improvement of postrelapse survival after 2005, the improvement has been minimal in the recent years and is similar to what we have observed in the current analysis. The marginal improvement in survival in this setting is likely due to access to new drugs such as pomalidomide, carfilzomib, daratumumab, and elotuzumab and other clinical trials. We are able to show the robustness of R-ISS in predicting postrelapse survival with R-ISS III patients showing a far inferior OS of 1.5 years compared to R-ISS I patients showing 4.5 years postrelapse survival.

In our cohort of patients with an early post-AHCT relapse, 2 groups were identified, those who had received maintenance post-AHCT (n = 127) or those who did not (n = 70). It is important to note that this analysis did not compare the rate of early relapse in maintenance versus nonmaintenance groups. However, the receipt of maintenance did not affect survival in the early relapse group or the median duration to relapse after AHCT. This speaks to the fact that disease biology driving early

Table 5
Univariate Analysis of Impact of Maintenance in the Early Relapse Group (Postrelapse OS in Maintenance versus No Maintenance)

	No Planned Postmaintenance (n = 127)		Planned Postmaintenance (n = 70)		
Best response post-transplant					
≥ VGPR	59 (46)		39 (56)		
< VGPR	68 (54)		31 (44)		
Median time to relapse after transplant (range)	10 (<1-24)		12 (1-24)		
	No. Assessable	Probability (95% CI)	No. Assessable	Probability (95% CI)	*P*
OS postrelapse	127		70		.86
1 yr		67 (59-76)		66 (54-77)	.82
2 yr		48 (39-57)		51 (39-64)	.67
3 yr		30 (21-39)		38 (24-53)	.33

Values are n (%) unless otherwise defined in the top part of the table and percents in the bottom part.

relapse is probably the most important prognostic factor, and newer strategies need to be devised for patients at risk of experiencing early relapse.

The year of transplant was not of prognostic significance in the early relapse group, although it was significant for OS in the entire cohort. A significant majority of patients in the era spanning 2012 to 2014 received maintenance and may reflect the improved survival from maintenance strategies. However, this improvement in survival did not accrue to the early relapse group and again reflects the aggressive biology of disease that led to early relapse. HCT-CI score and lines of pre-AHCT treatment remained significant predictors of postrelapse survival even among early relapses. Finally, we observed that early relapse patients who had received full–dose melphalan conditioning (200 mg/m^2) had inferior postrelapse survival compared with early relapse after lower dose melphalan (140 mg/m^2). Notably, melphalan dose was not correlated with OS in the entire cohort. This intriguing finding suggests that early relapse of MM despite full conditioning intensity may behave more aggressively. This analysis is unable to determine the mechanism of this phenomenon: that is, if early relapse after full melphalan dosage indicates relative refractoriness to subsequent therapies or clonal evolution with the addition of high–risk markers induced by high–dose melphalan in the setting of genomic instability or if there are other mechanisms mediating this observation.

A recent study by Kastritis et al. [23] reported prognosis of unselected patients who were treated with novel agents using R-ISS staging. The conclusion was verified that R-ISS is a robust tool for risk stratification of newly diagnosed patients with symptomatic myeloma.

Our analysis is limited by the relatively small sample size for the early relapse cohort. This may be reflective of the years of transplant that we studied when the R-ISS was not in full clinical use. The R-ISS was developed in 2015, whereas our dataset extending between 2008 and 2014 captures the real-world practice of MM patients receiving AHCT, and we remain optimistic that lactate dehydrogenase and fluorescent in situ hybridization studies will be more universally adopted.

In summary, we report that R-ISS at diagnosis predicts the risk of early relapse post-AHCT. Further, the outcomes of patients with R-ISS III disease continue to be poor even in the era of novel drugs in the setting of early relapse and maintenance. Finally, early relapse is a dynamic marker for high–risk disease and remains a therapeutic challenge, and future studies should also address the prevention of early relapse. Myeloma therapy continues to advance with newer modes of targeted therapies such as monoclonal antibodies, bispecific antibodies, chimeric antigen receptor T cells, and dendritic cell–based cancer vaccines [24]. Clinical trials targeting patients at risk for early relapse using such newer agents and novel combinations are necessary to effect a meaningful improvement in high–risk disease.

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