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Novel Prognostic Scoring System for Autologous Hematopoietic Cell Transplantation in Multiple Myeloma

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CONFLICTS OF INTEREST

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Abstract

We studied 2,528 patients with upfront AHCT for MM from 2008–2017 to develop a prognostic model to predict outcomes. High-risk cytogenetics included t (4;14), t (14;16), t (14;20), del13q on karyotype, del17p, +1q or 1pdel. A Cox model identified factors prognostic of progression/relapse in a training subset (N=1,246). A weighted score using these factors was assigned to a validation cohort (N=774). Presence of high-risk cytogenetics [hazard ratio, HR 1.68 (1.3–2.17)] and pre-AHCT bone marrow plasma cells (BMPCs) ≥10% [1.68 (1.33–2.12)] were assigned 4 points each; albumin at diagnosis <3.5 g/dl [1.31 (1.07–1.61)] 2; standard risk cytogenetics 1, and no cytogenetics abnormality, BMPCs <10% at AHCT and albumin ≥3.5 g/dl at diagnosis 0 points each. A three-category system with low risk (0–3), intermediate risk (4–8) and high risk (9–10) showed a 3-year PFS in the low vs. intermediate vs. high risk of 58% (95% CI 52–63) vs. 49% (95% CI, 43–56) vs. 31% (95% CI, 12–51), $p < .001$ respectively and 3-year OS in low vs. intermediate vs. high risk of 88% (95% CI 84–91) vs. 81% (95% CI 76–86) vs. 64% (95% CI 39–80); $p < .001$. Our prognostic scoring system can identify MM patients at risk for early relapse after AHCT.

Keywords

AHCT; MM; Prognostic Scoring System

Introduction:

Therapeutic options for the treatment of multiple myeloma (MM) have expanded greatly as result of new classes of drugs and better understanding of disease biology(1, 2). Despite these improvements, high dose therapy and autologous hematopoietic cell transplantation (AHCT) remains the preferred strategy for transplant eligible MM patients(3–5).

Current prognostic tools used in MM focus solely on disease-specific factors at diagnosis to determine patient prognosis—International Staging System (ISS)(6) and revised-ISS (R-ISS) (4). Limitations to both, the ISS and R-ISS, include the following: 1) they are not specific for HCT-eligible patients and do not consider other dynamic factors such as response to induction treatment that may predict disease biology, 2) if the LDH was not done at diagnosis, it is not possible to stage using the R-ISS(7), 3) the presence of other mutations, beyond the three targeted in the R-ISS i.e., del 17, t(4;14) and t(14;16) may identify patients at risk for early progression. Thus, there is room to further refine our risk staging system at the time of AHCT to better predict post-transplant outcomes. We therefore undertook this study using data from the Center for Blood and Marrow Transplant Research® (CIBMTR®) registry to identify disease-, patient-, and transplantation-specific variables to develop a risk

stratification tool that could be used to predict outcomes in patients undergoing AHCT for MM.

Methods:

Data Sources:

The CIBMTR is a research collaboration between The National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. It encompasses a voluntary working group of more than 500 transplantation centers worldwide. 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.

Patient Selection:

Patients who underwent upfront AHCT (defined as AHCT within 12 months of diagnosis) for MM in the U.S., from 2008–2017 using peripheral blood hematopoietic cells were included in the study. Patients that had concurrent amyloidosis, tandem AHCT allogeneic HCT, conditioning other than Melphalan (MEL) 200mg/m² were excluded. Patients who received thalidomide/dexamethasone or vincristine/adriamycin/dexamethasone induction were excluded as these do not represent practice in the US.

Definition and Response:

Responses were defined according to the International Myeloma Working Group (IMWG) criteria(8). Non-relapse mortality (NRM) was defined as death from any cause within the first 90 days or thereafter in the absence of relapse or progression. Progression free survival (PFS) was defined as time from transplantation to relapse, progression or death from any cause. Overall survival (OS) was defined as the time from transplantation to death from any cause. High risk cytogenetics was defined as the presence of one or more of the following: t (4;14), t (14;16), t (14;20), del 13q/monosomy 13 on karyotype, del 17p, 1q gain, 1p del.

Statistical analysis:

A total of 2,528 patients who underwent upfront AHCT for MM and met selection criteria were randomly assigned to a training data set comprising 50% of the cohort (n=1,246) and a validation data set including the remaining 50% of the patients (n=1,255). The training data set was used to develop a prognostic scoring system and the validation data set to assess the prognostic ability of the scoring system. A Cox proportional hazards model with stepwise selection procedure was used to select significant covariates for PFS. Forward-selection and backward-elimination procedures were used to confirm significant covariates. Interaction between significant covariates was examined and the proportional hazards assumption was examined. Based on the magnitude of the hazard ratio (HR) and regression coefficient associated with variables, a weighted score was assigned to factors associated with PFS

in the training cohort. Patients were grouped into low, intermediate and high-risk groups. Patients with missing data were included in the multi-variable Cox model analysis but were excluded from analysis of the risk score in the training and validation sets since they couldn't be assigned a score. Cause-specific HRs were reported in the analysis of the secondary endpoint: overall survival (OS).

Next, we compared this system with the R-ISS using a previously published CIBMTR cohort with available R-ISS data for predicting PFS using concordance index and kappa statistic(9).

Results:

Patients:

Table 1 shows the patient-, disease- and transplant-related variables between the training and the validation cohorts. As shown in the Table 1, the two groups were well balanced in terms of baseline characteristics. The median follow-up of survivors was 48 months (range, 1 to 129 months). The median age of the entire population was 59 years (range, 23 to 82 years) and 41% were females (Supplementary Table 1). High-risk cytogenetics population comprised 25% of the total population; 50% of patients in each group received bortezomib, lenalidomide and dexamethasone (VRD) as induction therapy. More than 50% of patients achieved very good partial response (VGPR) after induction, and 24% of patients used more than 1 lines of induction before proceeding to transplant.

Development of the CIBMTR scoring system

We constructed a Cox proportional hazards model using the training set that included the following variables: age, sex, race, Karnofsky performance score (KPS), hematopoietic cell transplantation comorbidity index (HCT-CI), cytogenetics, albumin, beta-2 microglobulin (β_2M), lactate dehydrogenase (LDH) at diagnosis, immunochemical subtype, serum creatinine at HCT, bone marrow plasma cells (BMPCs) at diagnosis and at HCT, disease status at the time of HCT and time from diagnosis to transplant.

Figure 1a summarizes the variables relevant to PFS identified in the multivariate analysis among 1,246 patients in the training set. We identified three major independent predictors of PFS: cytogenetics, BMPCs at HCT, and albumin at diagnosis. On the basis of the HRs and regression coefficients, we assigned a weighted score to the predictors: high-risk cytogenetics- 4 points; BMPC $\geq 10\%$ at HCT - 4 points; albumin at diagnosis <3.5 g/dL - 2 points; standard risk cytogenetics - 1 point; no cytogenetics abnormality, BMPCs $<10\%$ at HCT, and albumin ≥ 3.5 g/dL at diagnosis - 0 point. The overall score ranged from 0–10 with increasing scores indicating greater risk. Based on these data, we created a three-category CIBMTR scoring system: low risk - 0-3 points, intermediate risk – 4–8 points and high risk – 9–10 points. The HR for progression (using the low-risk group as the reference) was 1.74 (95% CI, 1.41–2.14); $p < 0.0001$ for the intermediate-risk group, and 3.77 (95% CI, 2.32–6.11); $p < 0.0001$ for the high-risk group (Table 2). The median PFS for those with low, intermediate and high risk was the following: 50 months (95% CI, 43–57), 29 months (95% CI; 24–35) and 14 months (95% CI, 3–24), respectively, $p < 0.001$. The 3-year

PFS estimates for those with low, intermediate and high-risk groups were 64%, 42% and 20% respectively (Figure 1b).

Variables not associated with PFS in the multivariate analysis included age, gender, race, HCT-CI, immunochemical subtype, disease status prior to HCT, KPS and time from diagnosis to HCT. Factors associated with PFS on univariate but not on multivariate analysis are shown in Supplementary Table 2.

Validation of the CIBMTR scoring system

We used the scoring system to calculate a risk score for individuals in the validation cohort for whom complete data on all three variables were available (Table 2). Complete data for all the variables were missing for 481 patients, leaving 774 patients for the analysis. Among these patients, the scoring system was prognostic for PFS (Table 2). The HR for progression was 1.21 (0.98–1.49); $p=0.07$ for the intermediate risk group and 2.06 (1.25–3.39); $p=0.004$ for the high-risk group, compared to low-risk. The median PFS for those with low, intermediate and high risk was: 42 months (95% CI, 37–51), 35 months (95% CI, 28–46) and 15 months (95% CI, 11–36); $p<0.001$. The 3-year PFS estimates for those with low, intermediate and high-risk groups were 68%, 49% and 31% respectively (Figure 1c).

Because the training set was developed based on PFS, and not on OS, we applied the score for OS in both training and the validation cohort for whom data were available for all three variables. The CIBMTR scoring system was prognostic for OS (Table 3). The HR for death (using low risk as a reference) was 1.44 (1.05–1.98); $p=0.02$ for the intermediate risk group, and 3.13 (95% CI 1.74–5.6); $p=0.0001$ for the high-risk group. The median OS in the low, intermediate and high risk was not reached, 98 months (95% CI, 75- NR) and 49 months (95% CI, 31–100); $p<0.001$ respectively. The 3-year survival estimates for those with low, intermediate and high-risk groups were 88%, 80% and 65% in the training cohort and 88%, 82% and 64% in the validation cohort, respectively (Figure 2a and 2b).

Comparison of the proposed scoring system with R-ISS

Next, we compared the CIBMTR scoring system with the R-ISS system in a second validation cohort of patients undergoing upfront AHCT with available R-ISS at diagnosis ($N=488$), previously reported by the CIBMTR(9). The 3-year PFS was 59% (95% CI, 52–64) in low risk group compared to 68% (95% CI, 59–75) in R-ISS I (Supplementary Fig 1A and 1B). We generated a cross table of our system (rows) with the R-ISS classification in the columns (Table 3). Based on the results of the kappa statistic, there was minimal agreement between the proposed scoring system and the R-ISS [0.13 (95% CI 0.07–0.18)]. Of 153 R-ISS I patients, 36 were up-staged to intermediate group by the CIBMTR scoring system, and of 49 R-ISS III patients, 48 were down-staged to low ($N=19$) and intermediate risk ($N=19$) groups. To quantify which prognostic system better fit actual post-transplant outcomes, we calculated the concordance index including 488 patients for whom complete data were available for R-ISS and the CIBMTR scoring system (Supplementary Table 3). We found the concordance index of the model to predict PFS be 0.57 and was comparable to 0.59 of R-ISS providing a complementary additional prognostic information of similar magnitude.

Discussion:

In this study, we present a novel scoring system able to prognosticate post-transplant outcomes in MM patients undergoing AHCT. Using readily available clinical data at the time of HCT, this simple tool identified low-, intermediate- and high-risk groups at the time of AHCT that had 3-year survival outcomes of 68%, 49% and 31% (PFS) and 88%, 82% and 64% (OS) respectively. Several prognostic tools are available for risk stratification in MM(10–12), but the most widely used is the ISS, and more recently the R-ISS(4, 6). Combining ISS with LDH and high-risk chromosomal abnormalities [del17p, t (4:14) and t (14:16)] at diagnosis, the R-ISS uses disease-related prognostic factors into risk stratification. Although R-ISS is prognostic of outcome after AHCT(9), it was not generated specifically for patients undergoing AHCT, and does not consider non-disease specific factors. Additionally, the R-ISS was derived from patients enrolled into experimental trials (65% of patients <65 years) and did not consider other high-risk abnormalities like chromosome 1(1q gain, 1pdel or both). A system developed based on patient-, treatment- and disease-related factors may offer further specificity to predict post-transplant outcomes. Thus, we developed the CIBMTR scoring system specifically for patients undergoing AHCT in the current era and considered other aforementioned factors for risk stratification.

Our analysis did not find an association between β_2 M and LDH on outcomes- important variables for ISS and R-ISS respectively(4, 6). LDH and β_2 M were missing in 57% and 23% of the patients respectively and could explain the lack of their impact on prognosis; however, both these variables were significant for PFS after adjusting missing values on univariate analysis but lost their significance on multivariate analysis. We used β_2 M and albumin separately into the model instead of ISS as staging was reported as either ISS and/or Durie-Salmon staging. Although the association between β_2 M and prognosis has been interpreted to reflect a higher tumor burden in myeloma(13, 14), it is important to realize that renal insufficiency may underline at least in part the higher levels of serum β_2 M seen in this disease, and thus may lack specificity in certain clinical situations.

Multiple myeloma is a heterogenous disease with nearly a quarter of patients experiencing median OS of 2–3 years and others with upwards of 10 years(7, 15–17). Even in the current era with several new treatment approaches, AHCT continues to play an important role in the treatment of MM(3, 18, 19). It is evident that patients relapsing early after AHCT have a poor outcome regardless of stage and cytogenetics at diagnosis(20–23). The R-ISS uses only 3 high-risk cytogenetic markers and it is now recognized that other mutations, such as 1q gain or amplification, 1pdel, t(14:20) likely represent other high risk markers(4). For the purpose of our study, we included all those specific cytogenetic lesions that have shown inferior outcomes and likely behave as high-risk disease. It is quite possible that these specific abnormalities may not be that relevant by itself, as combinations of cytogenetic lesions are more of a norm than exception and could have different prognostic impact on the outcomes as demonstrated in a recent study(24). In our recent CIBMTR studies,(7, 25) we have identified that nearly 60% of patients in the database representing the ‘real world’ practice do not have an LDH at the time of diagnosis further restricting the use of the R-ISS. Additional relevant post-diagnosis information includes response to induction, performance status, among others. This information available at the time of transplant can

be used to identify high-risk patients that could benefit from post AHCT consolidation and maintenance strategies. Previous studies have combined different prognostic tools in AHCT-eligible patients(10, 11) but these only included disease-specific factors at diagnosis and may not be able to identify those functional high-risk patients. Using our CIBMTR scoring system at the time of transplant, we identified high-risk patients with 3-year PFS of only 31%. These patients could be considered for clinical trials that include combinatorial immune and non-immune approaches.

About half of the patients in our study received VRD induction and is consistent with the results reported in previous studies(23, 26). This number is perhaps increasing in recent years owing to the changing landscape in induction regimens based on several phase III studies(27, 28). Interestingly, we did not find any association of pretransplant response on outcomes; however, we did find the BMPCs 10% as significant predictor for outcomes. This may represent a better surrogate for residual disease and chemoresistance than disease response as previously shown in a large retrospective study(29). Future studies are needed to study if achieving minimal residual disease (MRD) negativity at the time of HCT is associated with outcomes as current data suggest achieving MRD negativity post AHCT has been shown to be an important prognostic factor to predict post-transplant outcomes(30, 31). As MRD is being evaluated to its predictive values after induction, AHCT and consolidation/maintenance, it is possible to include this in future iterations of this prognostic system. Likewise, patients receiving >1 line of therapy prior to AHCT may reflect their underlying disease biology and chemoresistance. It is not clear from the data whether these patients received additional salvage therapy due to sub-optimal response to initial induction. Additional salvage therapy to achieve a “desired response” in those with less than partial response to induction has been shown to provide no benefit to survival after AHCT(32). We did not include induction regimen and lines of chemotherapy in our scoring system as there was no significant change in the score with or without the variable. Induction regimens in myeloma continue to evolve with VRD triplet being the standard now but may be replaced by newer triplets (e.g. Carfilzomib-RD, daratumumab-RD) or quadruplet induction in the near future(33). We believe our scoring system can be used to prognosticate patients undergoing AHCT regardless of the type of induction used. We also did not include line of therapy in our scoring system despite it being significant on analysis. The reason for this was practical. Myeloma patients may start initial treatment as inpatients. Lenalidomide is not available for use in the inpatient setting in the US. Thus, a patient may start with cyclophosphamide, bortezomib, dexamethasone (VCD) and switch in the following month to VRD as outpatient. This would be labeled as 2 lines of therapy. In order to avoid misattributing such situations, not wholly uncommon in MM, we opted to exclude this variable in our final scoring system.

The study has other limitations. About 30% of patients in our study were reported to have no FISH abnormalities. It is important to note that trisomic and IgH translocation MM comprise of 40% and 30% respectively, while 15% comprise of both and remaining are other abnormalities(34). It is possible the remaining patients were labelled as normal given the lack of appropriate probes for FISH, false negative FISH results, heterogenous FISH methodology and variable plasma cell enrichment as the results are dependent on the enrichment method. Thus, it is possible that the ‘no abnormality’ group includes patients

with both high and standard risk abnormality and bias outcomes. However, the superior outcomes seen in the low-risk cohort compared to high risk identify these groups as a separate group and may behave as a standard risk group. We included patients receiving only MEL 200 mg/m² for deriving the prognostic score which may limit the applicability of the score in patients older and/or less fit patients where the dose of melphalan is usually MEL140 mg/m² (35). However, in our second validation, the score was prognostic when applied to the second validation cohort which included patients with MEL140 mg/m² as well. In our analysis, the majority of patients were in low intermediate risk group (41% low-risk group, 52% intermediate risk) and this distribution may not represent better survival dissection among different groups, but the high risk groups were consistent with previous studies(4, 10). Like R-ISS, we identified cytogenetics as an important factor prognostic of outcomes(36), but the systems were similar in terms of prognostic capability. The magnitude of the benefit of both the scoring systems was limited (given that the concordance index was 0.57) suggesting that the incorporation of genomic aberrations or combining both scoring systems can further refine and complement our ability to prognosticate MM patients in the future.

Despite these limitations, the CIBMTR scoring system is of practical value to transplant physicians evaluating patients with MM for AHCT as it can be calculated with readily available clinical data at the time of AHCT. Most importantly, the scoring system may be used to identify high-risk populations where post-AHCT consolidation and maintenance may be of benefit and can be incorporated in future clinical trials to identify these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a 1b and 1c:
1a. Multivariable factors associated with PFS in the training cohort (bone marrow plasma cells BMPCs); 1b. PFS in the training cohort by prognostic scoring system risk classification; 1c. PFS in the validation cohort by prognostic scoring system risk classification

Figure 2a and 2b:
OS in the training and validation cohorts by prognostic scoring system risk classification

Table 1:

Comparisons between training and validation sets

Characteristics	Training set (1246)	Validation set (1255)	p-value
Median age, yrs.	58 (28–78)	59 (26–82)	0.58
Female	511 (41)	515 (41)	0.99
Race, white	808 (65)	814 (65)	0.98
KPS			0.70
90	683 (55)	707 (56)	
<90	538 (43)	526 (42)	
Missing	25 (2)	22 (1.7)	
HCT CI			0.44
0–2	866 (70)	839 (67)	
3	380 (30)	416 (33)	
Immunochemical subtype			0.64
IgG	716 (57)	742 (42)	
IgA	247 (20)	247 (20)	
Others*	283 (21)	277 (22)	
Serum albumin at diagnosis, g/dl			0.48
<3.5	418 (34)	420 (34)	
3.5	693 (56)	678 (54)	
missing	128 (10)	153 (12)	
Serum creatinine pre-HCT, mg/dl			0.14
<2 mg/dl	1084 (87)	1104 (88)	
2 mg/dl	155 (13)	147 (12)	
LDH at diagnosis			0.15
<upper limit	453 (37)	408 (33)	
>upper limit	106 (9)	109 (9)	
missing	680 (55)	734 (59)	
Beta-2 microglobulin at diagnosis, mg/L			0.10
<3.5	545 (44)	551 (44)	
3.5–5.5	201 (16)	192 (15)	
5.5	216 (17)	222 (18)	
missing	277 (22)	286 (23)	
BM plasma cells at transplant			0.65
<10	799 (64)	772 (62)	
10	208 (17)	209 (17)	
missing	232 (19)	217 (22)	
Disease status at transplant			0.44
CR/sCR	222 (18)	192 (15)	
VGPR	445 (36)	473 (38)	

Characteristics	Training set (1246)	Validation set (1255)	p-value
PR	493 (40)	510 (41)	
SD/PD/relapse	81 (6)	74 (6)	
Cytogenetics			0.38
Standard risk	430 (35)	467 (37)	
High risk	310 (25)	311 (25)	
No abnormality	380 (31)	369 (29)	
Unknown	126 (10)	108 (9)	
Lines of chemotherapy			0.31
1	934 (75)	973 (78)	
2	280 (22)	254 (20)	
missing	32 (3)	28 (2)	
Induction chemotherapy			0.84
VRD	626 (50)	627 (50)	
VTD/VCD/VD/RD	515 (42)	532 (42)	
Missing	105 (8)	96 (8)	

KPS: Karnofsky performance status, Hematopoietic cell transplantation co-morbidity index, I CR/ Scr: complete/stringent complete response, VGPR: very good partial response, PR: partial response, SD: stable disease, PD: progressive disease, VRD: velcade, lenalidomide and dexamethasone, TD: thalidomide and dexamethasone, others: Velcade, Cytosan and dexamethasone, lenalidomide and dexamethasone, Velcade, dexamethasone, Velcade, Thalidomide and dexamethasone

Table 2:

PFS by prognostic score in training and validation cohorts

	Training cohort			Validation cohort		
	N	HR (95% CI)	p-value	N	HR (95% CI)	p-value
Overall	793		<.0001	774		0.0003
Low (0–3)	456	1		432	1	
Intermediate (4–8)	316	1.74 (1.41–2.14)	<.0001	312	1.21 (0.98–1.49)	0.0709
High (9–10)	21	3.77 (2.32–6.11)	<.0001	27	2.06 (1.25–3.39)	0.0043

Table 3:

OS by prognostic score in training and validation sets

	Training cohort			Validation cohort		
	N	HR (95% CI)	p-value	N	HR (95% CI)	p-value
Overall	793		<.0001	774		0.0003
Low (0–3)	456	1		432	1	
Intermediate (4–8)	316	1.78 (1.32–2.39)	0.0001	312	1.44 (1.05–1.98)	0.0220
High (9–10)	21	4.64 (2.53–8.52)	<.0001	27	3.13 (1.74–5.63)	0.0001

Table 4:

Categorization of patients according to the proposed prognostic system and the revised international staging system

	Revised International Staging System (R-ISS)			Total
New scoring system	R-ISS I	R-ISS II	R-ISS III	
Low	117	171	19	307
Intermediate	36	109	29	174
High	0	6	1	7
Total	153	286	49	488