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IS THE INTERNATIONAL STAGING SYSTEM SUPERIOR TO THE DURIE SALMON STAGING SYSTEM? A COMPARISON IN MULTIPLE MYELOMA PATIENTS UNDERGOING AUTOLOGOUS TRANSPLANT

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1. CIBMTR data collection policy
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Abstract

The International staging system (ISS) for multiple myeloma (MM) is a validated alternative to the Durie Salmon staging system (DSS) for predicting survival at diagnosis. We compared these staging systems for predicting outcomes after upfront autologous stem cell transplantation by analyzing the outcomes of 729 patients between 1995 and 2002. With a median follow-up of 56 months the univariate probabilities (95% CI) of non-relapse mortality (NRM), relapse, progression free (PFS) and overall survival (OS) at 5 years were 7%, 68%, 25% and 52%, respectively. The median overall survival for stages I, II, III by DSS and ISS were 82, 68, 50 and 64, 68, 45 months, respectively. The concordance between the two staging systems was only 36%. Staging systems were formally compared using Cox models fit with DSS and ISS stages. Relative risks of PFS and OS were significantly different for stages I vs. II and II vs. III for DSS but only for stages II vs. III for ISS. Although both systems were predictive of PFS and OS; the DSS was superior in formal statistical comparison using Brier Score. However, neither system was strongly predictive of outcomes indicating the need for newer schemes incorporating other prognostic markers.

Keywords

myeloma; autologous hematopoietic stem cell transplantation; staging

INTRODUCTION

The Durie and Salmon system (DSS)(1) and the International Staging system (ISS)(2) are the most commonly used prognostic schemes in patients with newly diagnosed MM. The DSS uses the immunoglobulin levels, hemoglobin and calcium concentration and the number of bone lesions to predict tumor mass and estimate survival. Although several other staging systems (3–6) have been proposed since, the ISS based on the serum beta-2 microglobulin (Sβ2M) and albumin is the first to gain wide acceptance often superseding the DSS.

Compared to the DSS, the ISS is easier to compute, provides a more equal distribution of patients amongst the three disease stages and has been validated in subsequent studies(7). It is unclear whether higher ISS stages reflect higher MM tumor burden/aggressiveness or the level of target organ damage or both. Patients with a high ISS stage are at higher risk of

early death, but it is unclear whether this reflects an inability to receive and tolerate aggressive therapy or myeloma biology or both. Additionally, novel cytogenetic and gene expression profiling (GEP) markers, have been identified to predict outcomes independent of clinical stage(8). The ISS authors reported that while only 26% of their patients underwent upfront ASCT, their outcomes were equally well stratified by the ISS, compared to patients receiving non-transplant therapies. A smaller study(9) found that the ISS was better correlated with post transplant outcomes than the DSS although only a minority (16%) of the patients were in low DSS stages. No formal statistical comparisons of the ISS and DSS have been reported for patients receiving ASCT as initial therapy.

The existence of 2 staging systems with no mutually common parameters raises the possibility that they are both valid in differing situations. Also the outcomes of patients who are fit to undergo higher intensity therapy such as ASCT may be better predicted by tumor burden/tumor biology based staging system. We compared the relative utilities of the ISS and DSS stages at diagnosis in predicting post transplant outcomes in patients undergoing planned upfront ASCT for MM.

SUBJECTS AND METHODS

Data Sources

The CIBMTR is a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplants to a Statistical Center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee or the NMDP Coordinating Center in Minneapolis. (Details of data collection policy described in supplemental material)

Patients

Patients who underwent autologous peripheral blood and/or bone marrow stem cell transplantation for MM between 1995 and 2002 and reported to the CIBMTR, for whom both DSS stage and ISS stage were evaluable. The study population was limited to recipients of a melphalan based or busulfan and cyclophosphamide based conditioning regimen and having an interval from diagnosis to ASCT ≤12months (defined as an “upfront” ASCT). Plasma cell leukemia and patients receiving allogeneic transplants were excluded. ISS stages were assigned as described by Greipp et al(2) and DSS stages as described by Durie-Salmon et al(10). Since only a minority of patients with renal impairment underwent ASCT, the DSS sub-stage B was combined within the main numerical grouping for analysis.

Outcomes

Overall survival was defined as the time from date of transplant to date of death with survivors censored at the time of last contact. Non-relapse mortality (NRM) was defined as death occurring in the absence of relapse/progressive disease and summarized by the cumulative incidence estimate with relapse/progression as the competing risk. Relapse/progression was defined as the time to first evidence of laboratory recurrence or progression of myeloma according to the standard EBMT/IBMTR criteria(11) and summarized by the cumulative incidence estimate with NRM as the competing risk(12). Progression-free

survival (PFS) was defined as survival without progressive disease or relapse from CR. Progressive disease, relapse from CR and death in remission were considered events. Probabilities of survival and PFS were calculated using Kaplan-Meier estimator(13) and compared using the log-rank test.

STATISTICAL ANALYSIS

The primary objective was to compare DSS and the ISS stages at diagnosis as to their ability to predict transplant outcomes. The distribution of patients across the 2 systems and the agreement between stages in either system were compared using Cohen's Kappa statistic (14) expressed as a number between 0 and 1, with 1 representing complete agreement and 0 representing complete non-concordance(15). The ability of the stages assigned at diagnosis by the 2 staging systems to predict post ASCT survival and treatment failure (inverse of PFS) was compared. The relative risks (RR) of the main outcomes of interest were modeled using Cox proportional hazards regression. Risk factors potentially associated with treatment failure and survival were tested using Cox proportional hazards model(16). These variables are described in detail in the supplemental list. They included age by decade, gender, performance score, immunochemical subtype of MM, baseline creatinine, number of lines of pretransplant therapy, chemosensitivity at transplant, disease status at transplant, time from diagnosis to transplant, conditioning regimen, and year of transplant. Stepwise model building procedure was used to identify significant covariates that influenced outcomes.

Subsequent separate Cox models were created forcing the staging system (DSS or ISS) into the previous model and the Cox models fit with each stage were compared to identify which system allowed better discrimination between risk groups for PFS and survival. Adjusted probabilities of PFS and survival were calculated using the multivariate models, stratified by DSS stages and ISS stages, respectively, and weighted by the pooled sample proportion value for each prognostic factor in order to estimate the likelihood of outcomes in populations in similar prognostic group by the two staging systems. The relative risks (RR) of treatment failure and mortality (inverse of PFS and survival respectively) for stage II vs I and stage III vs II by DSS stages and ISS stages were calculated to compare the performance of prediction by the two systems.

The predictive accuracy of each system was then quantified. For each model evaluating DSS or ISS and survival or PFS, we estimated the percentage of explained variability (R^2) in predicting the probability of survival and PFS(17, 18) using a numerical score (Brier score) calculated for each staging system(19). The Brier score as a function of time assesses the predictive performance of a prognostic scheme. It is a measure of the inaccuracy of a prediction scheme and is calculated as the average deviation between predicted probabilities of events and their outcomes. Expressed as a number between 0 and 1; a score of 0 means the outcome was predicted with 100 percent certainty if we knew the staging system and a score of 1 indicated no prognostic benefit to knowing the stage. A smaller Brier score and a larger R^2 indicate better predictive performance.

RESULTS

Patient, Disease and Transplant Characteristics (Table 1a)

There were 729 patients from 138 centers with complete DSS and ISS staging (performed within a median of 15 days of diagnosis) and received ASCT within 12 months of diagnosis after Melphalan or Busulfan based conditioning therapy. Pretransplant characteristics and survival of patients with or without comprehensive staging data in the CIBMTR research database were similar. Pre-transplant patient, disease and transplant related characteristics of the study population are summarized in Table 1a. Patients were not exposed to lenalidomide or bortezomib as pretransplant therapy. Median follow up of survivors was 56 months.

Staging Distribution

The frequency distribution of patients across the DSS and ISS stages are summarized in Table 1b. Only 36% patients had concordant stages across systems. Within the DSS stage III patients, 30% were in ISS stage I, 41% in stage II and 29% in stage III. Conversely, amongst ISS stage III patients, 78% were DSS stage III, 20% DSS stage II and 2% DSS stage I. Agreement between the DSS and ISS stages calculated using Cohen's Kappa statistic was 0.085 (95% CI, 0.043 –0.126), indicating low concordance between DSS and ISS stages. Median survival estimates of patients within each stage group of either system sub-classified by stages of the alternate system are summarized in Table 1b.

Univariate and Multivariate Analysis of Autologous transplant Outcomes (Tables 2 and 3)

Univariate probabilities of NRM, relapse/progression, PFS/treatment failure and survival are summarized in Table 2. The relative risks of NRM, relapse/progression, treatment failure and mortality and the corresponding p values for stage II vs. I and III vs. II by DSS and ISS stages are given in Table 3.

Non-Relapse Mortality

Cumulative incidence of NRM at 1 year after ASCT was 5 (95% CI 3–6). In multivariate analysis, higher pretransplant serum creatinine was the only risk factor associated with NRM. Neither the DSS nor the ISS stages were significantly associated with NRM.

Relapse/Progression

Cumulative incidence of relapse/progression at 1, 3 and 5 years was 21% (95% CI 19–25), 53% (49–56) and 68% (64–72), respectively. Covariates significantly correlated with higher relapse/progression were the immunoglobulin isotype, disease state prior to transplant and interval from diagnosis to transplant. Higher DSS and ISS stages both predicted relapse. Higher RR of relapse/progression (RR=1.32, p=0.008) was observed for DSS stage III compared to stage II as well as stage II compared to stage I (RR=1.74, p=0.018). The ISS stage III compared to stage II was associated with higher risk of relapse/progression (RR=1.36, p=0.009) but not ISS stage II compared to stage I (RR=1.19, p=0.128).

Progression Free Survival and Treatment Failure

Higher DSS and ISS stages predicted treatment failure. Median PFS for stages I, II, III by DSS and ISS were 58, 31, 24 mo and 33, 27 and 23 months respectively. Probability of PFS at year 1, 3 and 5 for the entire cohort were 74 (95% CI 70–77), 41 (95% CI 38–45) and 25% (95% CI 21–29) respectively. Covariates significantly correlated with higher risk of treatment failure were lack of sensitivity to chemotherapy prior to transplantation, non responsive disease status pre-transplant and interval from diagnosis to transplant: The relative risk of treatment failure (RR=1.39, p=0.001) was higher for DSS stage III compared to stage II as well as stage II compared to stage I (RR=1.59, p=0.029). ISS stage III compared to stage II was associated with higher risk of treatment-failure (RR=1.30, p=0.019) but ISS stage II was not different compared to stage I (RR=1.22, p=0.063).

Survival and Mortality

Probability of survival for the cohort at 1, 3 and 5 years were 88 (95% CI 85–90), 68 (95% CI 65–72) and 52% (95% CI 47–56) respectively. Median survival for stages I, II, III by DSS and ISS were 82, 68, 50 months and 64, 68, 45 months respectively. Covariates correlated in multivariate analysis with higher risk of mortality were a higher creatinine prior to transplant, lack of chemosensitivity prior to transplantation and longer interval from diagnosis to transplant. Higher DSS and ISS stages both predicted mortality. Higher relative risk of mortality (p=0.006) was observed for DSS stage III compared to stage II (RR=1.41, p=0.006) as well as stage II compared to stage I (RR=1.78, p=0.038). ISS stage III compared to stage II was associated with higher risk of mortality (RR=1.46, p=0.007) but not ISS stage II compared to stage I (RR=1.10, p=0.482). These results were unchanged even after restricting the analysis to patients who received ASCT within 9 months of diagnosis.

Statistical Comparison of DSS and ISS schema

The RRs for treatment failure and mortality, for stage II vs I and III vs II by DSS stages and ISS stages are shown in Table 3. The DSS stage system allowed better discrimination between risk groups compared to a Cox model fit with ISS stages (Table 3, figures 1–2). For both outcomes, DSS stages II vs I were better discriminators of risk than ISS stages II vs. I. The percentage of explained variability (R^2) between the 2 staging schemes for 1, 3 and 5 year PFS and OS probabilities were calculated using Brier scores (Table 3). Although the R^2 (measure of explained variability) was low for both systems, the DSS system had slightly higher R^2 at 1, 3 and 5 years for PFS and OS compared to the corresponding R^2 for ISS. Brier scores for the PFS and OS at 1, 3 and 5 years were marginally lower for the DSS compared to the ISS. The higher R^2 and lower Brier scores indicate superior predictive capability of the DSS over the ISS although of small magnitude.

DISCUSSION

For a biologically heterogeneous disease, it is unlikely that any one clinical staging system can fully accommodate the factors that impact outcomes. ASCT is established as one of the standards of care in patients with newly diagnosed MM (20, 21). In this cohort of patients receiving ASCT, intrinsic disease related factors (as opposed to host factors) are likely to

have a higher relative contribution to treatment failure since patients with advanced co-morbidities are less likely to undergo transplant.

The DSS focuses on variables correlated with myeloma mass(1) whereas the ISS evolved from a statistical model focusing on survival duration(2). The lack of common prognostic variables in the 2 staging systems, explains the low 36% concordance in stage assignment and the low Kappa correlation. The distribution of patients by ISS stage in our study (35%, 42% and 23% in stages I, II and III respectively) was similar to the original ISS data of Greipp et al. (28%, 33% and 39 % of patients in corresponding ISS stages)(2). Similarly the DSS stage distribution of our study population (7%, 32% and 62% in stages I, II and III respectively) was similar to the DSS stages in the ISS database (8%, 26% and 63% for stages I, II and III respectively). Although the utility of ASCT in DSS stage I patients is controversial, their presence in the cohort reflects prevalent clinical practice. Median survival estimates for stages I, II, III by DSS and ISS were 82, 68, 50 and 64, 68, 45 mo, respectively. These compare with median survival estimates for stages I, II and III in the original ISS database at 62, 58 and 45 mo for DSS and 62, 44 and 29 months for ISS, respectively. Median survivals of the ISS stages I, II and III receiving ASCT in the Greipp dataset were 111, 66 and 45 months respectively.

In multivariate analyses, we adjusted for the impact of significant covariates in addition to the staging system to obtain a true measure of the impact of the stage on outcomes. Both systems discriminated adequately for stages II and III, with higher RRs correlating with higher stage. However DSS better discriminated lower risk patients providing a sharper separation of DSS stage I from stage II compared to ISS stages I and II. It is possible that DSS stage I patients have better survival than the ISS stage I patients who constituted a larger subset (35% of patients). Among DSS stage I patients, only 1% were ISS stage III whereas 18% of ISS stage I patients were in DSS stage III representing a higher risk subgroup with shorter survival (Table 1b). Within each of the DSS stage groups, subgroups of ISS stages I and II patients had similar survivals. Thus low DSS stage better discriminated the best prognostic cohort.

Since our database consists entirely of transplant recipients, there is an inherent bias excluding older patients (median age 56 vs. 60 years in this database vs. the original ISS database) and those with substantial co-morbidities. The Sβ2M and albumin used in ISS are composite measures of disease burden and its impact on the host. The Sβ2M indirectly reflects tumor mass, renal function and possibly immune function whereas the albumin levels are a reflection of diverse host factors including nutrition, liver function, effect of interleukin-6 on the liver, systemic inflammation and renal protein loss. It is possible that patients with host factors that produce higher ISS stages were lacking in our database since they may not have been considered for ASCT. Also high risk patients who may have died early would have been excluded biasing the study toward better risk patients although these biases apply equally to both ISS and DSS staging schema. The DSS in our analysis was a robust staging system that predictably discriminated all 3 stages by post ASCT outcomes. The ISS was not a significant improvement in terms of predictive ability.

Krejci et al(22) compared the DSS and ISS stages in 133 patients and reported that ISS stage 3 but not higher DSS stages was correlated with poor post transplant survival. Interestingly, they found no significant difference in outcomes between ISS stages I and II. A limitation of this study was the under-representation of patients in DSS stages I and II. Tao et al(23) reported that in 206 patients receiving chemotherapy based regimens, the DSS stages accounted for statistically significant survival differences between all 3 stages whereas the ISS did not discriminate between stages I and II. Our study is the largest comparison of the DSS and ISS in persons receiving upfront ASCT and the only formal statistical comparison of the predictive accuracy of the 2 staging systems.

The ISS is a major improvement over the DSS in that it separates patients into cohorts using easily measurable, objective and reproducible parameters. However in patients who are aggressively treated using upfront ASCT, the ISS does not improve the prediction of post transplant outcomes compared to the DSS. It is not clear whether the ability to receive an autotransplant overrides the effect of stage especially for stages I and II in the ISS. The Brier score and R^2 comparisons demonstrate that the predictive inaccuracies of both systems are similar with neither of these staging systems predicting the heterogeneity in patient outcomes very well. If this lack of predictability for stage is an effect of the aggressive therapies received, it is possible that novel anti-myeloma agents may also have a similar impact on the natural history of disease. Most importantly these data demonstrate the need for new staging schema. Incorporating some of the other known prognostic factors such as cytogenetics, MRI and PET imaging studies and gene expression profiles to modify the ISS might define biologically relevant prognostic groups better.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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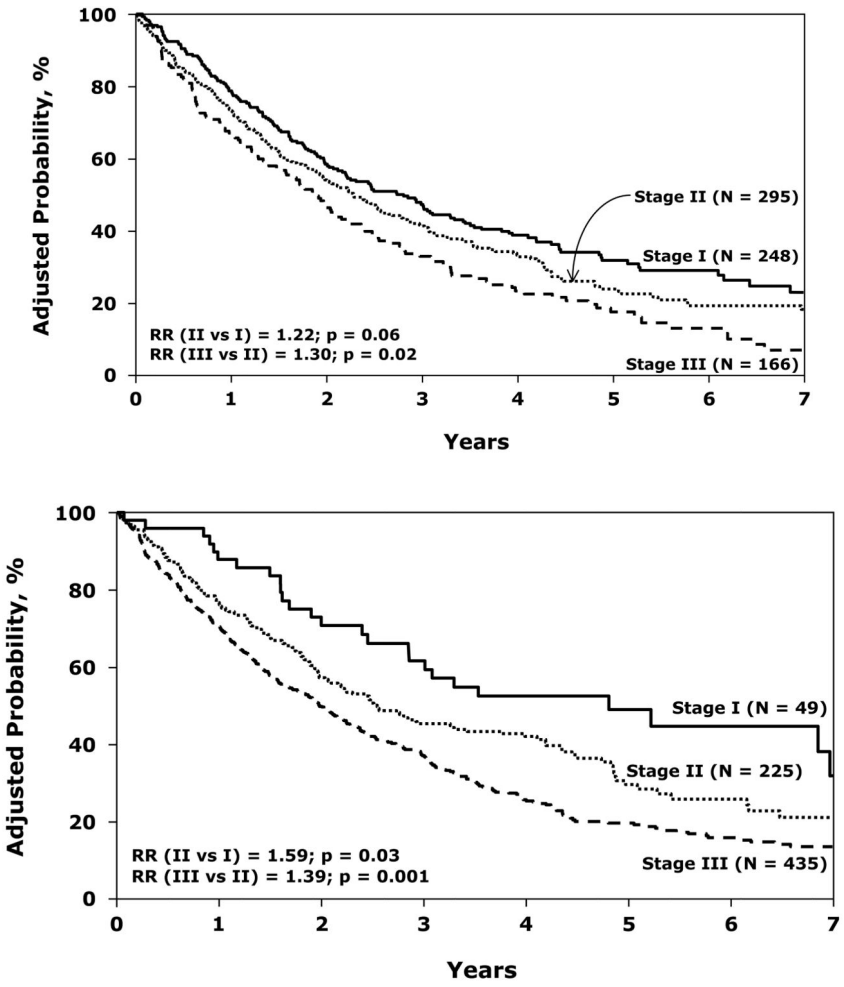

Figure 1.

Adjusted probabilities of progression-free survival after upfront autologous stem cell transplantation for Multiple Myeloma, by International Staging System (A) and Durie-Salmon System (B).

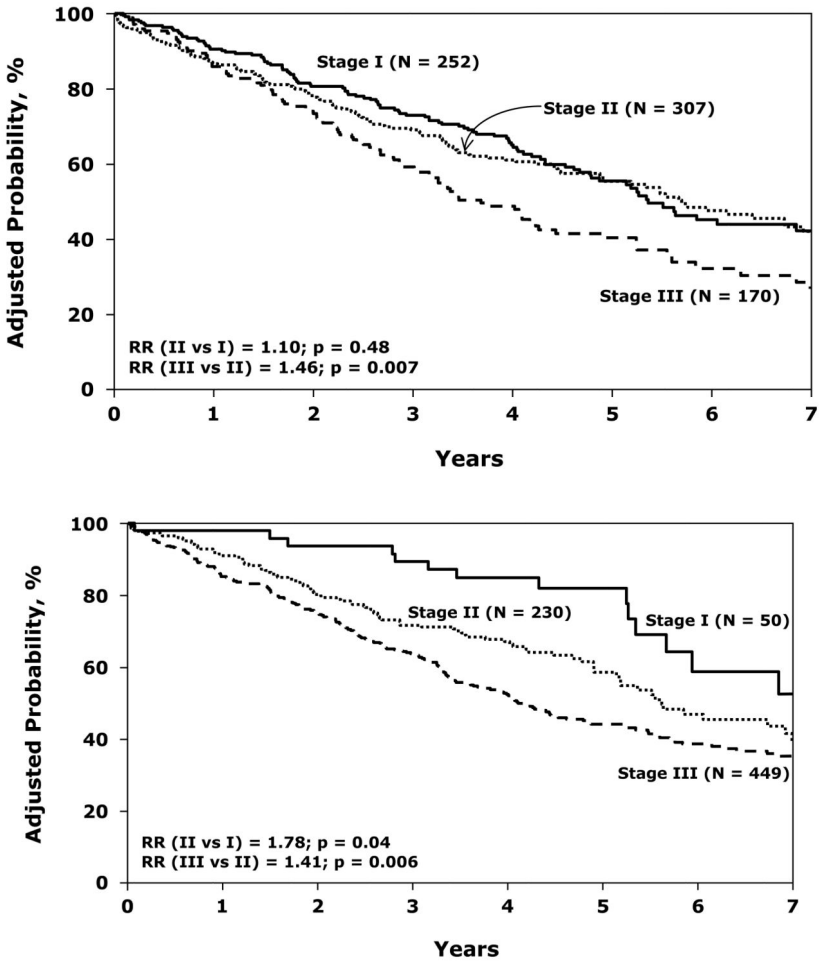

Figure 2.

Adjusted probabilities of overall survival after upfront autologous stem cell transplantation for Multiple Myeloma, by International Staging System (A) and Durie-Salmon System (B).

Table 1

Table 1a. Characteristics of 729 patients who received ASCT for Multiple Myeloma after melphalan-based or busulfan and cyclophosphamide- based conditioning regimens, reported to the CIBMTR between 1995 and 2002.

Variable	N eval	N (%)
Age, median (range), years	729	56 (27 – 76)
Male sex	729	442 (61)
Karnofsky score pretransplant ≤80	709	273 (39)
Disease related		
Immunochemical subtype of myeloma	714	
IgG/A/D		413/145/5 (58/20/1%)
Light chain		117 (16)
Non-secretory		32 (5)
Creatinine at diagnosis ≥ 2 mg/dL	700	108 (15)
Lytic bone lesions anytime prior to transplant	609	504 (83)
Prior chemotherapy regimens	728	
Alkylator based (Melphalan/Cyclophosphamide)		169 (23)
VAD±similar		504 (69)
Thalidomide±others		41 (6)
Others[a]		14 (2)
Number of lines of chemotherapy	728	
0 –1		509 (70)
2		185 (25)
>2		34 (5)
Sensitivity to chemotherapy prior to transplant	712	
Sensitive		584 (82)
Resistant		128 (18)
Disease status prior to transplant	710	
Complete/partial remission		583 (82)
Minimal response/no response/stable disease		105 (15)
Relapse/Progression		22 (3)
Transplant related		
Time from diagnosis to transplant, median (range), months	729	7 (2 – 12)
Conditioning regimen	729	
Melphalan alone		431 (59)
Melphalan±TBI±others		210 (29)
Bu+Cy±others (not TBI, not melphalan)		88 (12)
Number of Transplants	729	
1 transplant, 2nd not planned		623 (85)
2 transplant, 2nd not planned		43 (6)
2 transplant, 2nd planned tandem		63 (9)

Table 1b. Correlation of DSS and ISS & Median Survival by ISS and DSS stages:				
Median Survival by ISS Subgroups within each DSS stage:				
DSS	**ISS**	**N (%)**	**OS mo**	**Median OS by ISS stage mo**
I	I	**26 (4)**		82
	II	20(3)	82	93
N=50 (7%)	III	4(1)		52
II	I	92(13)	68	70
	II	**104(14)**		81
N= 230 (32%)	III	34(5)		59
III	I	134(18)	50	49
	II	183(25)		66
N=449 (62%)	III	**132(18)**		41
Median Survival by DSS Subgroups within each ISS stage:				
ISS	DSS	N(%)	OS mo	Median OS by DSS stage mo
I	I	26(4)		82
	II	92(13)	64	70
N=252 (35%)	III	134(18)		49
II	I	20(3)		93
	II	**104(14)**	68	81
N=307 (42%)	III	183(25)		66
III	I	4(1)		52
	II	34(5)	45	59
N=170(23%)	III	**132(18)**		41
Concordant Stage		**36%**		
Cohen’s Kappa		0.085 (95% CI, 0.043–0.126)		

Abbreviations: VAD = vincristine+dexamethasone+adriamycin; MP = melphalan+prednisone; Bu = busulfan; Cy = cyclophosphamide; TBI = total body irradiation; Eval = evaluable; PBSC = peripheral blood stem cells; BM = bone marrow. Completeness index FU = 90%.

[a]Other chemotherapy regimens were: adryamicin+vincristine+etoposide (n=1), adryamicin+vincristine (n=10), adryamicin alone (n=1) and prednisone alone (n=1).

3 (6%), 22 (10%) and 83(19%) of patients were in substage B within DSS stages 1, II and III.

Table 2

Univariate analyses among patients who underwent who received autologous transplants for Multiple Myeloma receiving a melphalan-based or busulfan and cyclophosphamide- based conditioning regimens and within 12 months of diagnosis, by staging system.

Outcome:	DSS % (95%CI)	ISS % (95%CI)	P-value
Non-relapse mortality @ 1 yr			
Stage I	2 (0–8)	4 (2–6)	0.49
Stage II	3 (1–6)	6 (4–10)	0.07
Stage III	6 (4–8)	3 (1–6)	0.11
Progression-free survival			
Stage I			
@ 3 years	60 (46–74)	46 (40–53)	0.09
@ 5 years	47 (32–62)	31 (24–37)	0.05
Stage II			
@ 3 years	45 (39–52)	42 (36–47)	0.42
@ 5 years	29 (22–36)	24 (18–30)	0.33
Stage III			
@ 3 years	37 (33–42)	33 (26–41)	0.39
@ 5 years	20 (15–24)	18 (11–25)	0.62
Overall survival			
Stage I			
@ 3 years	89 (79–96)	73 (67–78)	0.003
@ 5 years	81 (68–92)	55 (48–62)	<0.001
Stage II			
@ 3 years	72 (66–78)	70 (64–75)	0.55
@ 5 years	59 (51–66)	56 (49–62)	0.55
Stage III			
@ 3 years	64 (59–68)	59 (51–66)	0.25
@ 5 years	44 (39–50)	39 (31–48)	0.33

Table 3

Relative Risks (95% CI) of post transplant outcomes from Cox model incorporating ISS and DSS respectively and Brier score and R^2 (higher R2 and lower Brier score indicate superior prediction).

	Relative Risks			
	ISS		DSS	
Outcome[1]:	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**
NRM[3]		0.426[2]		0.167[2]
II vs I	1.38 (0.73 – 2.61)	0.319	0.68 (0.21 –2.18)	0.516
III vs II	0.64 (0.29 – 1.40)	0.262	1.97 (0.97 –4.01)	0.061
Relapse/Progression[4]		0.001[2]		<0.001[2]
II vs I	1.19 (0.95 – 1.48)	0.128	1.74 (1.10 –2.74)	0.018
III vs II	1.36 (1.08 – 1.72)	0.009	1.32 (1.08 –1.62)	0.008
Treatment-failure[5]		0.001[2]		<0.001[2]
II vs I	1.22 (0.99 – 1.50)	0.063	1.59 (1.05 –2.43)	0.029
III vs II	1.30 (1.04 – 1.62)	0.019	1.39 (1.14 –1.69)	0.001
Overall mortality[6]		0.003[2]		<0.002[2]
II vs I	1.10 (0.85 – 1.42)	0.482	1.78 (1.03 –3.08)	0.038
III vs II	1.46 (1.11 – 1.91)	0.007	1.41 (1.11 –1.80)	0.006
	Brier score and R^2			
	ISS		DSS	
	Brier Score	R^2	Brier Score	R^2
PFS				
1 year	0.1860	1.2%	0.1855	1.4%
3 years	0.2343	1.3%	0.2323	2.1%
5 years	0.1846	1.1%	0.1818	2.6%
Survival				
1 year	0.1021	0.2%	0.1003	1.9%
3 years	0.2082	1.1%	0.2052	2.5%
5 years	0.2419	0.8%	0.2345	3.8%

[1] Details of variables tested in the Cox model are described in the supplemental data

[2] Two degree freedom test

[3] Other significant covariate for NRM was creatinine prior to transplant.

[4] Other significant covariates for relapse/progression were: immunochemical subtype of myeloma, disease status prior transplant and time from diagnosis to transplant.

[5] Other significant covariates for treatment failure (inverse of PFS) were: sensitivity to chemotherapy prior to transplantation, disease status prior transplant and time from diagnosis to transplant.

[6] Other significant covariates for survival (mortality) were: creatinine prior to transplant, sensitivity to chemotherapy prior to transplantation and disease status prior transplant.