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ORIGINAL ARTICLE

Early relapse post autologous transplant is a stronger predictor of survival compared with pretreatment patient factors in the novel agent era: analysis of the Singapore Multiple Myeloma Working Group

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The clinical outcome of multiple myeloma is heterogeneous. Both the depth of response to induction and transplant as well as early relapse within a year are correlated with survival, but it is unclear which factor is most relevant in Southeast Asian patients with multiple myeloma. We retrospectively analyzed outcomes of 215 patients who were treated with upfront autologous transplant in Singapore between 2000 and 2014. In patients who received novel agent (NA)-based induction, achieving only partial response (PR) post-induction was associated with poorer OS (HR 1.95, $P = 0.047$) and PFS (HR 2.9, $P < 0.001$), while achieving only PR post-transplant was strongly correlated with both OS (HR 3.3, $P = 0.001$) and PFS (HR 7.6, $P < 0.001$), compared with patients who achieved very good partial response (VGPR) or better. Early relapse was detected in 18% of all patients, although nearly half had initially achieved VGPR or better post-transplant. Early relapse after NA-based induction led to significantly shorter OS (median 22 months vs not reached, $P < 0.001$), and was strongly associated with OS (HR 13.7, $P < 0.001$). The impact of suboptimal post-transplant response and early relapse on survival may be more important than pretransplant factors, such as International Staging System or cytogenetics, and should be considered in risk stratification systems to rationalize therapy.

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INTRODUCTION

The incidence of multiple myeloma is increasing rapidly in Asia, including Singapore.[1] Novel antimyeloma agents (bortezomib, thalidomide, lenalidomide) incorporated into induction therapy before high-dose therapy and autologous stem cell transplant (ASCT) have significantly improved survival in patients over the past decade, as evidenced from several randomized trials and retrospective series in Europe and United States.[2] Although a similar trend is evident in Asian patients, there is a paucity of data on the impact of novel agents on transplant outcomes among Asian myeloma patients.[3] Biologically, multiple myeloma is a spectrum of diseases and the implication of response to novel agents can be variable in different ethnicities. A clearer understanding of which prognostic factors are most relevant in Asian myeloma patients in the novel agent era can improve risk stratification and therapeutic decision making.

Available evidence shows a strong association between depth of response pretransplant and post-transplant PFS, and in some studies, overall survival (OS).[4–7] However, the outcomes of the group of patients who respond are heterogeneous; some patients relapse within a year and have very poor survival despite achieving deep responses.[8–10] It is unknown whether depth of response or early loss of response is a more important predictor of survival as both factors have not been compared directly in studies. This information is relevant for deciding when to intensify therapy (e.g. pretransplant, post-transplant or at relapse), especially since additional treatment can pose toxicity risks without significant benefit.

In view of these uncertainties, we undertook a retrospective analysis to evaluate survival data of newly diagnosed multiple myeloma patients referred to two tertiary centers in Singapore who were treated with both conventional and novel induction therapy before high-dose therapy-ASCT between 2000 and 2014. We sought to compare the prognostic significance of depth of response and early relapse on survival outcomes in Asian patients.

MATERIALS AND METHODS

Patient selection, variables definition

From the myeloma registry of the Singapore Multiple Myeloma Study Group, we evaluated survival data of 215 newly diagnosed and untreated myeloma patients who received ASCT at two tertiary centers in Singapore and started treatment between 1 January 2000 and 1 June 2014. Patients who received more than one line of induction therapy ($n = 28$), or who did not achieve at least partial response (PR) ($n = 9$) before transplant, were excluded from the analysis. Staging was carried out according to the International Staging System (ISS), and patients were grouped based on whether they received conventional agents or novel agents for induction. Patient characteristics are shown in Table 1. Patients received induction with four cycles of chemotherapy before transplant.

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Table 1. Clinical characteristics of patients with multiple myeloma treated with autologous stem cell transplant

Characteristic of patients	*Non-novel agent induction (n = 52)*	*Novel agent induction (n = 163)*	*Overall (n = 215)*
Age (years) at time of transplantation (median, range)	53, 30–73	56, 34–72	55, 30–73
Race; n (%)			
Chinese	43 (83)	83 (51)	126 (59)
Malay	1 (2)	33 (20)	34 (16)
Indian	2 (4)	20 (12)	22 (10)
Others	6 (11)	27 (17)	33 (15)
Gender, male	32 (62)	91 (56)	123 (57)
ISS stage at diagnosis; n (%)			
1	8 (15)	31 (20)	39 (18)
2	15 (29)	60 (37)	75 (35)
3	37 (71)	72 (44)	101 (47)
Cytogenetics by FISH (n = 112); n (%)			
Low or standard risk	0 (0)	90 (55)	90 (42)
High risk	0 (0)	22 (13.5)	22 (10)
Missing	52 (100)	51 (31.3)	103 (48)
Time from diagnosis to ASCT; months, range	10.6, 1.6–20.2	8.4, 1.7–19.7	9.0, 1.6–20.2
Post-induction response; n (%)			
CR	13 (25)	58 (36)	71 (33)
VGPR	3 (6)	42 (26)	45 (21)
PR	36 (69)	63 (38)	99 (46)
Post-transplant response; n (%)			
CR[a]	38 (72)	81 (50)	119 (55)
VGPR	1 (2)	44 (27)	45 (21)
PR	13 (25)	38 (23)	51 (24)

Abbreviations: ASCT = autologous stem cell transplant; CR = complete response; ISS = International Staging System; PR = partial response; VGPR = very good partial response. [a]In patients receiving non-novel agent-based induction, CR includes near CR as per the European Group for Blood and Marrow Transplant criteria.

The most common non-NA chemotherapy used was Vincristine, doxorubicin and dexamethasone, while the most common NA regimen was thalidomide and dexamethasone or bortezomib, cyclophosphamide, and dexamethasone. Cyclophosphamide and G-CSF were used to mobilize stem cells. Melphalan at a dose of 200 mg/m^2, or adjusted to 140 mg/m^2 if serum creatinine clearance < 50 mL/min, was administered in two doses on days -3 and -2, followed by ASCT. Disease response was assessed after induction treatment, and at 100 days after transplant according to the International Myeloma Working Group uniform response criteria and the European Bone Marrow Transplant response criteria for patients transplanted before 2006,[11,12] and classified as PR, very good partial response (VGPR) and complete response (CR). High-risk cytogenetics by FISH was defined as the presence of 17p13 deletion, t(14;16) or t(4;14).[13] FISH data were available in 112 patients (69%) of the novel agent (NA) cohort, and was not available in patients who did not receive NA. Overall survival (OS) was defined as the length of time between diagnosis and date of death. Patients without a recorded death date were censored for OS at their last contact date. PFS was defined as the length of time between diagnosis until progression or the date of death. Patients who did not have a documented progression or death date were censored for PFS at their last contact date. Early relapse was defined as relapsing within 12 months of transplant date. Approval for review of these records was obtained from the respective center's Institutional Review Board and was in accordance with the Declaration of Helsinki.

Statistical analysis

The chi-squared and Fisher's exact two-sided tests were used for comparisons between categorical variables and the *t*-test was used for continuous variables. *P*-values are two-sided, and $P < 0.05$ was considered to reflect statistical significance. Survival probabilities were calculated using the Kaplan–Meier estimator, with log-rank analysis used to compare between different groups. Multivariate analysis was performed using the Cox proportional hazard regression model. Variables analyzed included age at diagnosis (continuous), gender, race (other nationalities vs Singaporean Chinese, Malay, Indian), ISS stage III vs I/II, cytogenetics high risk vs standard or low risk, NA use, time from diagnosis to transplant $\leqslant 12$ months vs > 12 months, post-induction response and post-transplant response. Forward stepwise variable selection at a 0.2 significance level was used to identify covariates to build the eventual multivariate model. In the model, the assumption of proportional hazards was tested using a time-dependent covariate, and all variables considered in the multivariate analysis satisfied the proportionality assumption. Univariate and multivariate analyses were performed using logistic regression with early relapse by 12 months as the end point to identify variables prognostic for early relapse. All analyses were performed using Stata (Statacorp, College Station, TX, USA).

RESULTS

Between 2000 and 2014, 215 patients (57% male) received an autologous transplant at a median of 9.0 (range 1.6–20.2) months after diagnosis. Seventy-six percent of patients received NA (lenalidomide, thalidomide or bortezomib) before autologous transplant. The median estimated follow-up of patients was 89 months from ASCT. Patient characteristics are further elaborated in Table 1. Significantly more patients achieved response of VGPR or better after NA-based induction therapy than after non-NA induction therapy (65% vs 31%, $P < 0.001$). For the non-NA and NA groups, median OS was 58 and 97 months, $P = 0.023$, while median PFS was 54 vs 57 months, $P = 0.505$. An explanation for an improved OS without significantly different PFS in the NA group is that more than 90% received effective therapy after progression (e.g. lenalidomide which has significant activity in patients refractory to thalidomide), while only 15% of patients in the non-NA group received NA (mainly thalidomide) after relapse. In addition, the European Group for Blood and Marrow Transplant criteria used to determine progression in the non-NA group required a repeat investigation of the serum monoclonal paraprotein and did not use free light chain as a progression criterion, which could have increased the time to progression.' Overall, 44 and 45% of patients, in the non-NA and NA group, respectively, achieved better response after transplant.

In our cohort, there were no significant differences in outcomes between patients who achieved CR or VGPR post-induction or post-transplant, although there was a trend towards improved OS and PFS in patients who achieved CR as compared with VGPR. Outcomes in both response categories were thus reported together. In univariate analysis, patients with ISS III vs I/II disease or who achieved only PR post-transplant compared with CR/VGPR had worse OS and PFS. Patients with high-risk cytogenetics or who achieved only PR post-induction compared with CR/VGPR had worse PFS but not OS.

Multivariate analysis in subgroups receiving NA induction adjusting for age, race and ISS showed that achieving only PR post induction was associated with poorer OS and PFS. The respective median OS was 97 vs 85 months ($P = 0.031$), while the median PFS was 80 vs 32 months ($P = 0.001$), in patients who achieved post-induction response of VGPR or better vs patients who achieved PR. Achieving PR post transplant was even more strongly associated with both poorer OS (HR 3.33) and PFS (HR 7.56) compared with achieving VGPR/CR (Table 2). The respective median OS was not reached vs 67 months ($P = 0.003$), while the respective median PFS was 78 vs 13 months ($P < 0.001$), in patients who achieved the post-transplant response of VGPR/CR

Table 2. Multivariate analysis for overall and PFS

Parameters	*Overall survival*		*PFS*	
	HR (95% CI)	P	*HR (95% CI)*	P
Novel agent based induction (n = 163)				
Post-induction response PR vs CR/VGPR	1.95 (1.01–3.88)	0.047	2.90 (1.69–4.96)	< 0.001
ISS III vs I/II	1.29 (0.62–2.67)	0.322	2.19 (1.27–3.76)	0.005
Post-transplant response PR vs CR/VGPR	3.33 (1.60–6.92)	0.001	7.56 (4.06–14.08)	< 0.001
High-risk cytogenetics vs standard/low risk[a]	1.59 (0.56–4.53)	0.382	2.28 (1.06–4.89)	0.034
Early relapse within 12 months	13.7 (6.06–30.62)	< 0.001		
Traditional agent induction (n = 52)				
Post-induction response PR vs CR/VGPR	1.16 (0.55–2.47)	0.693	1.29 (0.62–2.67)	0.493
ISS III vs I/II	3.13 (1.45–6.78)	0.004	4.49 (1.88–10.72)	0.001
Post-transplant response PR vs CR/VGPR	1.42 (0.57–3.58)	0.454	1.12 (0.45–2.780	0.811
Early relapse within 12 months	5.1 (2.28–11.17)	< 0.001		

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; ISS = International Staging System; PR = partial response; VGPR = very good partial response. Variables with $P < 0.2$ in the univariate analysis were included in the multivariate model, namely age, race, ISS stage, high-risk cytogenetics, post-induction response, post-transplant relapse and early relapse. [a]High-risk cytogenetics defined as 17p13 deletion, t(14;16) or t(4;14), analyzed in subset of 112 patients with available FISH data.

vs PR (Figure 1). Initial low ISS stage (I or II) was associated with improved PFS (median 81 vs 40 months, $P = 0.004$), but not correlated with OS. Among patients who received non-NA-based induction, multivariate analyses indicate that neither post-induction nor post-transplant responses were associated with PFS and OS. Only initial low ISS stage (I or II) was associated with improved OS and PFS. When analyzed in the subgroup with available FISH data, adverse cytogenetics was only associated with PFS in multivariate analysis (HR 2.28, $P = 0.034$), and not correlated with OS.

Early relapse at 12 months was detected in 18% of all patients and 37% of patients who relapsed. Among this subgroup with early relapse, 60 and 52% did not achieve VGPR post-induction and post-transplant, respectively, 72% were in ISS III at diagnosis and 56% had unfavorable cytogenetics. Patients who experienced early relapse within one year had significantly worse median OS (median 16 vs 122 months, $P < 0.001$), and multivariate analysis show that early relapse was independently associated with poorer OS in both patients who received non-NA or NA induction regimens (HR 5.1 and HR 13.7, respectively). There was a nonsignificant trend towards reduced risk of early relapse with NA (16% vs 24%, OR 0.61, $P = 0.234$).

Logistic regression analysis was performed to identify risk factors predicting relapse within 12 months post transplant. In patients who received NA-based induction, multivariate analysis indicated that only higher ISS stage (HR 4.7, 95% CI 1.5–11.2, $P = 0.0071$) and PR post-transplant (HR 5.6, 95% CI 1.5–10.9, $P = 0.01$) were prognostic for early relapse. High-risk cytogenetics was associated with early relapse in multivariate analysis in the subset of patients with available FISH data (OR 5.0, 95% CI 1.01–24.5, $P = 0.047$). In patients who received non-NA-based induction, only higher ISS stage was associated with early relapse in multivariate analysis (HR 9.8, 95% CI 1.2–13.4, $P = 0.034$). We also examined whether different salvage regimens post relapse affected survival. In patients who had not received novel agents previously, significantly longer post-relapse survival was achieved via treatment with thalidomide, bortezomib or lenalidomide based regimens, with a median post-relapse survival of 31 vs 5 months (HR 3.4, 95% CI 1.0–12.2, $P = 0.046$). However, there were no significant differences in post-relapse survival among patients who had received NA-based induction and a different NA at relapse (median post-relapse survival was 11 months).

DISCUSSION

Our study in a Southeast Asian population show that novel agent induction led to high response rates $\geqslant$VGPR (62%), which translated into high CR and VGPR rates post transplant. Like prior studies, achieving at least VGPR with novel induction led to improved PFS, although the impact on OS was of borderline significance. High-dose therapy-ASCT further deepened responses in a proportion of patients, and post-transplant response $\geqslant$VGPR was more robustly associated with PFS and OS than post-induction response. Of note, among the patients who relapsed within a year, almost half had initially achieved VGPR post transplant. Patients who suffered early relapse have a dismal post-relapse survival of 11 months despite salvage therapy, and present an unmet therapeutic challenge.

Achieving responses of VGPR or better after novel agent induction was associated with improved PFS, and weakly correlated with OS in our study. These findings are similar to the IFM 2005-01 study, which demonstrated significantly longer PFS but not OS for patients achieving VGPR or better post-induction.[14] A number of studies since have further reported that achievement of CR or stringent CR was associated with improved long-term outcomes when compared with lesser degrees of response with NA induction.[4,7] Despite these reported associations, additional pretransplant salvage chemotherapy in patients who did not achieve PR post-induction did not improve OS or PFS, even when deeper pretransplant responses were achieved.[15] The different implications of post-induction response reported across studies may reflect differences in study population, underlying disease heterogeneity in myeloma or the weaker predictive value of post-induction response. On the other hand, the depth of post-transplant response appears to be more consistently associated with survival outcomes in prior studies.[5] Our retrospective analysis also show robust associations between post-transplant response $\geqslant$VGPR and both improved PFS and OS in the novel agent era.

Despite achieving good responses post transplant, about 50% of patients in our cohort still relapsed within one year ('unsustained response'), with very dismal outcomes. These findings are similar to Kumar *et al.*,[8] who showed that patients who relapse within a year after ASCT have poor prognosis, with median OS of 10.8 months from the time of relapse. More recently, Jimenez-Zepeda *et al.*[9] showed, in a cohort of patients receiving novel agent induction, a significantly shorter median OS in patients who relapsed within a year vs after (20 vs 93 months), findings comparable to our observations. Multivariable analysis

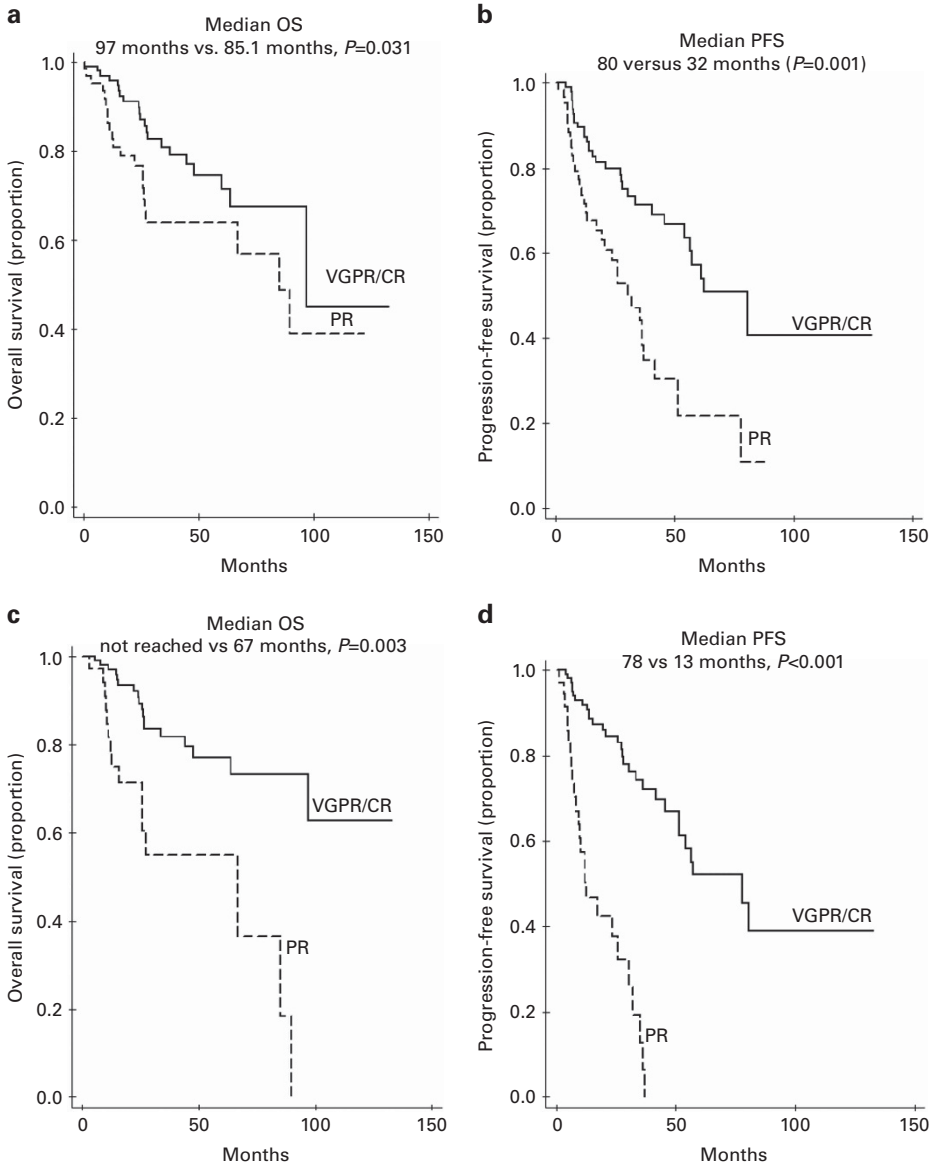

Figure 1. Achieving only partial response to novel agent induction leads to shorter overall survival (**a**) and PFS (**b**) compared with achieving VGPR/CR. Achieving only partial response to autologous transplant after novel agent induction leads to significantly shorter overall survival (**c**) and PFS (**d**).

showed that higher ISS stage, achieving only PR post transplant, and adverse cytogenetics were factors predictive of early relapse; however, the model could only predict about 38% of the variance in the data. Evidently, more markers are needed to improve risk stratification to identify this group of patients who relapse early after induction regimens containing novel agents. This population may have inherent biologic characteristics that do not respond well to a single autologous transplant.

Lastly, our observations that the old ISS may be less robust in the novel agent era (only associated with PFS/early relapse but not OS) parallel findings by prior studies,[16] and support the use of the revised ISS, which includes adverse cytogenetics, for risk stratification.[17] However, the prognostic impact of adverse cytogentics (17p13 deletion, t(14;16) or t(4;14)) needs to be clarified further. While the Spanish GEM2000 trial found that these FISH abnormalities were independently associated with unsustained CR and OS,[18] Jimenez-Zepeda *et al.*[9] did not observe associations of abnormal cytogenetics with early relapse, which the authors attributed to incomplete genetic data. Our findings were that adverse cytogenetics were associated with early relapse and PFS but not OS. Further work is needed to validate these and other genetic markers, for more accurate risk stratification in myeloma patients.

Limitations of our study include the retrospective, non-randomized nature of our study that limits the scope of its conclusions. Analyses may be underpowered in the group of patients receiving non-novel agent induction. Thirdly, post-transplant maintenance was given to 21.8% of our cohort as per treating physician's preference, and may potentially confound the observed associations. However, when multivariate Cox regression analysis was repeated incorporating the use of maintenance therapy, results were not different. Fourthly, comprehensive cytogenetic data were not available in our cohort, limiting our ability to analyze the effects of hypodiploidy, gain of 1q and loss of 1p on survival outcomes.[19] Lastly, in a proportion of patients diagnosed before 2006, the European Group for Blood and Marrow Transplant response criteria were used, and the categories did not include VGPR, which may have affected

associations analyzed in the pre-novel agent era. However, all patients who had novel agent-based induction were assessed using International Myeloma Working Group response criteria, hence our main conclusions should not be affected.

In conclusion, myeloma treatment has evolved and quality of response is associated with survival in patients in Southeast Asia. Although maximizing response is an important end point, 18% of patients relapse early of which nearly half were in VGPR or better post-transplant. Early relapse appears as an important treatment-related factor independent of, and more significant than, higher ISS stage or high-risk FISH markers in determining survival in our series. Therefore, more effective risk stratification markers are needed to identify patients before early relapse, and novel management strategies are needed to prevent early relapse.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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