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Research Article

Induction Therapy with Novel Agents and Autologous Stem Cell Transplant Overcomes the Adverse Impact of Renal Impairment in Multiple Myeloma

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ABSTRACT

We investigated the impact of renal impairment (RI) on the outcome in multiple myeloma (MM) patients following induction and autologous stem cell transplantation (ASCT). Among 349 patients who received a first ASCT for MM, 86 (24.6%) had RI at diagnosis, defined as estimation of glomerular filtration rate (eGFR) <40 mL/min/1.73 m^2 according to the modification of diet in renal disease (MDRD) formula. Post induction reversal of renal function occurred in 68 (79%) patients including complete renal response in 37.2%. Two hundred and fifty-one patients had received novel agents for induction; posttransplant complete response (CR) rates were 71.4% for patients with renal impairment (RI) versus 67.2% in those without RI, $p = 0.23$. The quality of stem cell collection and days to engraftment were similar except that patients with RI required higher transfusion numbers of packed red cells ($p < 0.002$) and platelets ($p < 0.007$). The median overall survival (OS) was 96 months (95% confidence interval [CI] 72.80–119.20) for patients with eGFR ≥40 mL/min, $n = 195$) versus 62 months (95% CI 28.7–95.3) for 56 patients with RI (eGFR <40 mL/min), $p = 0.15$. The 5-year OS was 64.6% versus 54.4%, respectively. The median progression-free survival (PFS) was 52 months (95% CI 36.3–67.7) for patients with eGFR ≥40 mL/min versus "not reached" for those with eGFR <40 mL/min $p = 0.87$; and the 5-year PFS was 48.1% versus 51%, respectively. We conclude that induction with novel agents results in reversal of renal dysfunction in the majority of patients. Consolidation with Hemopoietic Stem Cell Transplantation (HSCT) overcomes the adverse impact of RI on survival.

1. INTRODUCTION

Renal impairment (RI) in multiple myeloma (MM) is present in approximately 20% to 30% of patients at diagnosis as defined by the Durie-Salmon staging criteria (serum creatinine >2 mg/dL) [1–3]. Renal function is better assessed by estimation of glomerular filtration rate (eGFR) by the modification of diet in renal disease (MDRD) formula ($eGFR_{MDRD}$) [4] and has been adopted by the International Myeloma Working Group (IMWG) [5]. Patients with eGFR of less than 40 mL/min/1.73 m^2 are generally considered to have an inferior outcome [6]. A number of studies have reported reversal of renal function in 50% to 80 % of patients. These studies have used cytotoxic chemotherapy, for example vincristine, adriamycin and dexamethasone (VAD as continuous infusion over 4 days) [2], in earlier years and novel agent-based induction in recent years [3,7–11]. Major experience has been in the nontransplant setting with improved outcome in those with reversal of renal function. Some studies have also reported on the impact of RI on outcome in the transplant setting with variable results [7–21]; a few of these have included patients with severe RI or those on hemodialysis [20,21]. While most of these studies are from West, there are only case reports or small series from other parts of the world with little information on the use of $eGFR_{MDRD.}$

To determine the long-term outcome of MM patients with RI, who received induction therapy followed by high-dose chemotherapy and stem cell transplant, we have performed a comprehensive analysis with regard to baseline characteristics, engraftment kinetics,

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toxicity, response to induction therapy, and to the transplant and long-term outcome. This report describes these results.

2. PATIENTS AND METHODS

In this retrospective analysis, all patients with MM who underwent first autologous stem cell transplantation (ASCT) between January 1995 and December 2016 were included. RI was defined as an eGFR rate <40 mL/min/1.73 m^2 and estimated using the MDRD formula (available online https://www.mdcalc.com/mdrd-gfr-equation [22]). Patients were grouped into three categories:

i. Patients who had normal renal functions (eGFR ≥40 mL/min) at diagnosis and at transplant (Group A),

ii. Patients who had RI at diagnosis (eGFR <40 mL/min), which improved to ≥40 mL/min after induction therapy prior to transplant (Group B)

iii. Patients who had RI at diagnosis and continued to have an eGFR <40 mL/min prior to transplant (Group C)

Transplant Protocol: The detailed transplant protocol has been described elsewhere [23]. For conditioning, high-dose melphalan at 200 mg/m^2 was administered; patients with RI received melphalan at a dose of 140–160 mg/m^2. Transplant response was evaluated on day 100 ± 1 week as per European Group for Blood and Marrow Transplantation (EBMT) criteria [24]. Patients were given maintenance therapy using low-dose thalidomide (50 mg daily) or lenalidomide (5–10 mg/day for 21 days every month) or bortezomib (2 mg subcutaneously, twice a month). In addition, patients with an eGFR ≥60 mL/min also received zoledronic acid once every 3 months for the first 2 years and then once in 6 months indefinitely, along with calcium and vitamin-D supplements.

3. DEFINITIONS AND STATISTICAL ANALYSIS

Response to transplant was defined as per the EBMT criteria [24]. Renal response to induction therapy was defined as per the model established and described earlier by Ludwig *et al.* [25] and the IMWG [5] Briefly, a complete renal response (CRrenal) was defined as a sustained (at least 2 months) improvement in baseline eGFR from <50 to ≥60 mL/min; a partial renal response (PRrenal) was defined as a sustained improvement in base line eGFR from <15 mL/min to 30–59 mL/min; a minor renal response (MRrenal), a sustained improvement in base line eGFR from <15 mL/min to 15–29 mL/min or from 15–29 mL/min to 30–59 mL/min [5]. Overall survival (OS) was defined as the time from date of transplant until death or date of censor (30th November, 2018). Progression-free survival (PFS) was calculated from date of transplant to disease progression or death (regardless of the cause of death). Descriptive statistics (median and range) were calculated for all variables. The prognostic factors for response to transplant were analyzed using the Pearson Chi-square test and binary logistic regression analysis. Survival curves were plotted according to the method of Kaplan and Meier and were compared using the log rank test. The prognostic factors for survival were analyzed using Cox regression analysis. Analyses were performed using SPSS-16 statistical software. Analysis was by intention-to-treat. The study was approved by the Institution's Ethics Committee.

4. RESULTS

Patients' characteristics are shown in Table 1. The median follow-up for the whole group was 82 months (range 23.5 to 30.3 months). The median age was 52 years (range, 29 to 68 years) and 236 (67.6%) were male, 34.7% had International Staging System stage III (ISS III) disease, and 24.4% had Durie-Salmon stage IIIB disease. Eighty-one (23.7%) patients had light chain myeloma. Two hundred and fifty-one (71.9%) patients had received novel agents for induction, 21.5% had received VAD (as continuous infusion), and the remaining 23 (6.6%) had received alkylating agent-based induction. 35.9% of patients had received more than one induction regimen prior to transplant. The median interval from diagnosis to transplant was 10 months (range, 2–128 months).

4.1. Induction Treatment

Novel agent-based induction therapy: 178 (70.9%) had received a two-drug combination: thalidomide-dexamethasone (Td, *n* = 92), lenalidomide-dexamethasone (Rd, *n* = 54), and bortezomib-dexamethasone (Vd, *n* = 32). A three-drug combination was used by 73 patients (VTd: *n* = 23, VRd: *n* = 23, VCd: *n* = 21, Pad: *n* = 1 (Vd and liposomal doxorubicin). Another group of five patients received other thalidomide-based combinations).

4.2. Renal Impairment (RI) at Presentation and Its Reversibility with Induction Therapy

The median serum creatinine and $eGFR_{MDRD}$ were 1.9 mg/dL (0.2–23.60 mg/dL) and 68.7 mL/min (1.66–182.0 mL/min), respectively. RI as defined by serum creatinine (>2 mg/dL) and $eGFR_{MDRD}$ were 22.4% and 24.64%, respectively. Thirteen (3.7%) patients were dialysis-dependent at the time of diagnosis. Patients with RI were more likely to be female. More patients had ISS III, DSS IIIB, lower Hb (≤10 g/dL), lower serum albumin (<3.5 g/dL), hypercalcemia (>11.5 mg/dL), light-chain myeloma, and a longer interval (>12 months) from diagnosis to transplant. More patients had received alkylating agent-based induction therapy. The pretransplant status (sensitive versus resistant) was not significantly different among the three groups (Table 1).

Reversibility of RI was observed in 68 out of 86 patients (79%). The renal response as per IMWG criteria was as follows: CR renal (*n* = 32, 37.2%), PR renal (*n* = 16, 18.6%), MR renal (*n* = 21, 24.4%). Twelve out of 13 patients who required dialysis initially, became dialysis-independent (Supplementary Table S1).

4.3. Renal Function at Transplant

The median serum creatinine and $eGFR_{MDRD}$ were 0.9 mg/dL (0.49–6.10 mg/dL) and 81 mL/min (5–187.8 mL/min), respectively. Patients with serum creatinine >2 mg/dL and eGFR < 40 mL/min were 3.2% and 5.4%, respectively.

Two hundred and sixty-three patients (75.6%) who had eGFR ≥40 mL/mt at diagnosis, continued to have eGFR ≥40

Table 1 Patients baseline characteristics.

Variable	Group A N = 263		Group B N = 68		Group C N = 18		p Value
	No	%	No	%	No	%	
Age (years)							
Median	52		53		50.5		0.459
(range)	29–68		29–65		31–60		
Gender							
Male	185	70.3	43	63.2	8	44.4	0.05 (overall)
Female	78	29.7	25	36.8	10	55.5	A vs B + C = 0.04
ISS							
I	100	38.9	2	2.9	1	5.6	0.001 (overall)
II	110	42.8	11	16.2	-	-	A vs B + C = 0.001
III	47	18.3	55	80.9	17	94.4	B vs C = 0.233
DSS							
≤IIIA	257	98.1	6	8.8	0	-	0.001
IIIB	05	1.9	62	91.2	18	100.0	A vs B + C =.001
Ig type *N* = 342							
IgG	166	63.6	29	45.3	9	52.9	0.073
IgA	40	15.3	15	23.4	2	11.8	A vs B + C = 0.027
K + L chain	35 + 20	21.1	13 + 7	31.3	2 + 4	35.3	
EM disease							
Yes	62	23.6	15	22.1	3	16.7	0.782
No	201	76.4	53	77.9	15	83.3	
Hb (G/dL)							
≤10G/dL	126	47.9	59	86.8	16	88.9	0.001
>10G/dL	137	52.1	9	13.2	2	11.1	A vs B + C = 0.001
S.Album in (G/dL)							
<3.5	91	40.1	38	55.9	11	61.1	0.001
≤3.5	172	59.9	30	44.1	7	38.9	A vs B + C = 0.001
BM-PC% *N* = 348							
<40	140	53.4	32	47.1	8	44.4	0.527
≤40	122	46.6	36	52.9	10	55.6	
S.Calcium mg/dL N = 324							
≤11.4	237	96.3	50	73.5	9	50.0	0.001
≤11.5	9	3.7	13	19.1	6	33.3	A vs B = 0.001
Induction treatment							
Novel *	195	74.1	47	69.1	9	50.0	0.008 (overall)
VAD	57	21.7	13	19.1	5	27.8	A vs B + C = 0.07
Alk.agents	11	4.2	8	11.8	4	22.2	
Pre-tx status							
Sensitive	216	82.1	61	89.7	14	77.8	0.263
resistant	47	17.9	7	10.3	4	22.2	
Interval months							
≤12	173	65.8	38	55.9	9	50.0	0.161
>12	90	34.2	30	44.1	9	50.0	A vs B + C = 0.04
Inducti on regimen, *N* = 348							
One line	174	66.4	41	60.3	8	44.4	0.131
>one line	88	33.6	27	39.7	10	55.6	A vs B = 0.211
Tx in first vs second remission							
Primary	190	72.2	44	64.7	11	61.1	0.330
Post salvage	73	27.8	24	35.3	07	38.9	

ISS = international staging system; DSS = Durie and Salmon staging; BM PC = bone marrow plasma cell%.
**Novel agents-based induction therapy (N = 251):* 178 (70.9%) had received two drug combination; thalidomide + dexamethasone (Td, *N* = 92), lenalidomide + dexamethasone (Rd, *N* = 54), and bortezomib + dexamethasone (Vd, *N* = 32). A three-drug combination was used in 73 patients (VTd-23, VRd-23, VCd-21, PAd-1 (Vd + liposomal doxorubicin)- 1 and 5 patients had received thalidomide-based combinations.

mL/min pretransplant (Group A). Of the 86 patients with RI, eGFR improved to ≥40 mL/min in 68 (79.0%) patients (Group B) and the remaining 18 (21.0%) continued to have an eGFR <40 mL/min (Group C).

4.3.1. Engraftment kinetics (Table 2)

The number of stem cell harvests, median CD34 counts, and time to engraftment (neutrophil and platelet) were not significantly different among the three groups. Patients with RI required a higher rate of transfusion of packed red blood cell (RBC) ($p < 0.002$) and platelets ($p < 0.007$), prolonged use of antibiotics ($p = 0.06$), and longer hospitalization ($p = 0.06$) (Table 2). Oral mucositis (all grades) was more frequent in patients with RI (Groups B and C); $p < 0.01$. Hemodialysis during transplant was required in 5.1% of patients with RI as compared to 1.3% with normal renal function. Day +100 transplant-related mortality was significantly higher among patients with RI (Groups B and C) compared to Group A: 9/86 (10.5%) versus 9/263(3.4%), $p < 0.01$.

Table 2 | Engraftment characteristics.

	All Patients N = 349	Group A N = 263	Group B N = 68	Group C N = 18	p Value
Stem cell graft: CD34 counts × 10(6)/kg					
Median	2.67	2.60	2.72	2.91	1 vs 2 = 0.498
Range	0.30–16.7	0.30–16.7	0.52–15.5	1.39–7.6	2 vs 3 = 0.581
					1 vs 3 = 0.407
No of stem cell harvest					
Median	2	2	2	2	0.190
Range	1–6	1–6	1–4	1–4	
Days for ANC ≥500/cmm					
Median	11.0	11.0	11.0	11.0	1 vs 2 = 0.402
Range	1–37	1–37	9–28	9–18	2 vs 3 = 0.364
					1 vs 3 = 0.640
Days for platelet counts ≥20,000/cmm					
Median	13.0	12.0	13.0	13.0	1 vs 2 = 0.691
Range	0–58	0–58	7–40	7–21	2 vs 3 = 0.95
					1 vs 3 = 0.941
Days of fever					
Median	5.0	4.0	5.0	6.0	1 vs 2 = 0.313
Range	0–29	0–29	0–24	2–16	2 vs 3 = 0.600
					1 vs 3 = 0.917
Days of antibiotics					
Median	9.0	8.0	10.0	11.0	1 vs 2 = 0.069
Range	0–37	0–37	0–33	5–17	2 vs 3 = 0.621
					1 vs 3 = 0.501
Days of hospitalization					
Median	17.0	17.0	19.0	17.0	1 vs 2 = 0.075
Range	8–70	9–70	11–44	8–31	2 vs 3 = 0.927
					1 vs 3 = 0.012
Packed red blood cells					
Median	1.0	1.0	2.0	2.0	1 vs 2 = 0.002
Range	0–12	0–12	0–10	0–5	2 vs 3 = 0.709
					1 vs 3 = 0.244
Single donor platelets					
Median	3.0	3.0	3.0	3.0	1 vs 2 = 0.007
Range	0–16	0–16	0–15	1–15	2 vs 3 = 0.558
					1 vs 3 = 0.002
Days for G-CSF post Tx					
Median	12	12.0	12.50	12.0	1 vs 2 = 0.313
Range	0–37	0–37	0–30	8–21	2 vs 3 = 0.038
					1 vs 3 = 0.001

ANC = absolute neutrophil count; Tx = transplant.

4.3.2. Response to transplant (Table 3)

Overall, 213/349 (61%) patients achieved complete response (CR) posttransplant, 62 (17.8%) had very good partial response (VGPR), 42 (12%) had partial response (PR). Fourteen (4.1%) patients had stable disease and 5.2% had died of transplant-related complications. Among patients with pretransplant VGPR, 70.0% achieved CR posttransplant, the CR rate was 45.5% for patients in PR, 23% for those with stable disease, and 12.5% for patients with progressive disease pretransplant.

For Group A : Overall response rate (CR + VGPR + PR) was 93.5%, compared to 86.7% for Group B and 65.7% for patients in Group C, $p < 0.001$ (Group A versus Group B, $p = 0.326$, Group B versus C, $p < 0.03$, Group A versus B + C, $p < 0.006$) (Table 3).

4.4. Pretransplant Renal Response Versus Posttransplant Myeloma Response

Among 32 patients with CRrenal, 21 (65.6%) achieved hematological CR posttransplant as compared to 56.3 % (9/16) among PRrenal and 47.6% (10/21) among those with MRrenal (Supplementary Table S2). One patient who was dialysis-dependent underwent ASCT in CR followed one year later by a renal transplant; she is currently dialysis-independent and continues to be in stringent CR [26].

5. SURVIVAL

The median OS for all 349 patients from date of transplant was 91.5 months (95% confidence interval [CI] 72.6–110.4); 97 months (95% CI 70.1–123.9) for Group A, 30 months (95% CI 13.8–46.3) for Group B, and 37 months (95% CI 5.0–69.0) for Group C, $p < 0.0005$ (Figure 1).

The median PFS for all patients from date of transplant was 43 months (95% CI 34.6–51.4); 46 months (95% CI 36.3–55.7) for Group A, 30 months (95% CI 13.8–46.3) for Group B, and 22 months for Group C, $p = 0.14$ (Figure 2).

Novel agent-based induction and impact of RI on outcome:

Among 251 patients who received novel agent-based induction combinations (doublet, $n = 178$) and triplet, $n = 73$), the

Table 3 Response to transplant.

Pretransplant	No. of Patients	Posttransplant				
		CR	VGPR	PR	Stable	Died
CR	119 (34.1)	110 (92.4)	4	-	1	4
VGPR	60 (17.2)	42 (70.0)	14	1	-	3
PR	112 (32.1)	51 (45.5)	30	20	6	5
Stable	26 (7.4)	6 (23.1)	10	7	-	3
Progressive disease	32 (9.2)	4 (12.5)	4	14	7	3
Total	349	213 (61.0%)	62 (17.8)	42 (12.0)	14 (4.0)	18 (5.2)

Posttransplant Response	Group A (*N* = 263)		Group B (*N* = 68)		Group C (*N* = 18)		*p* Value
	N	%	*N*	%	*N*	%	
CR	163	62.0	41	60.3	9	50.0	
VGPR	49	18.6	12	17.6	1	5.6	$P < 0.001$ Group A vs B
PR	34	12.9	06	8.8	2	11.1	$P = 0.326$ Group B vs C
Stable	10	3.8	4	5.9	-	-	$P < 0.03$ Group A vs B + C
Died	7	2.7	5	7.4	6	33.3	$P < 0.006$

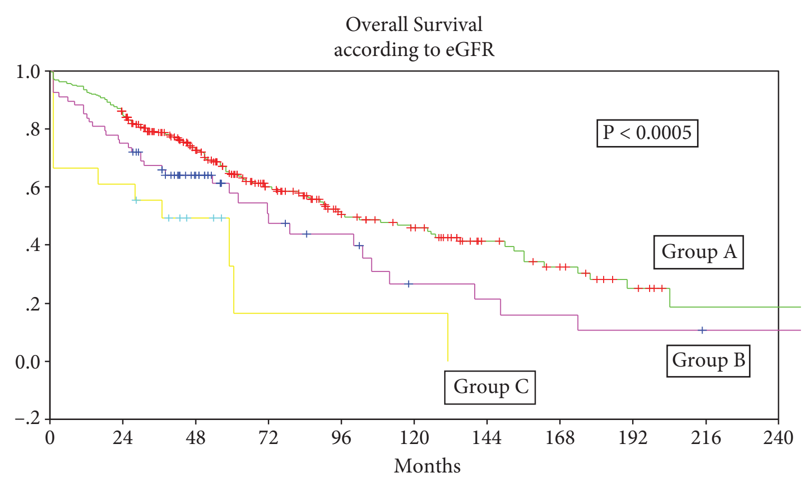

Figure 1 Group A: Patients with normal renal functions (estimation of glomerular filtration rate [eGFR] ≥40 mL/mt) at diagnosis and at transplant, *n* = 263, Group B: Patients with eGFR <40 mL/mt at diagnosis and ≥40 mL/mt prior to transplant, *n* = 68, Group C: Patients with eGFR <40 mL/mt at diagnosis and prior to transplant, *n* = 18.

post-transplant response rate (CR + VGPR) was similar; 83.1% versus 84.9%, p = ns. The median OS was 95 months (95% CI 79.87–110.13) versus not reached, p = ns) and median PFS was 56.5 months (95% CI 36.7–76.3) versus 45.50 months (95% CI 38.04–52.96, p = ns), for the two groups (doublet versus triplet combination), respectively.

With respect to RI posttransplant, overall response rates (CR + VGPR + PR) were 91.1% (51/56) patients with RI versus 93.3% (182/195) without RI; p = ns, CR rates were 71.4% (n = 40) versus 67.2 % (n = 131) respectively, p = ns (Supplementary Table S3). Median OS was 96 months (95% CI 89.4 to 110.0) in Group A versus 62 months (95% CI 28.7 to 95.3) in Group B + C, p = ns. Five-year OS was 64.6% versus 54.4% in Group A versus Groups B + C, respectively (Figure 3). The corresponding median PFS was 52 months (95% CI 36.3–67.7) in Group A versus 'PFS not reached' in Groups B + C, p = ns. Five-year PFS was 48.1% versus 51% for Group A versus Groups B + C, respectively (Figure 4).

5.1. Predictors of OS: Univariate Analysis

For Group A patients, predictors of OS included ISS III ($p < 0.02$), presence of extramedullary disease ($p < 0.001$), low serum albumin (<3.5 G/dL) ($p < 0.0001$), treatment with novel agents ($p < 0.009$), treatment with one induction regimen ($p < 0.001$), primary versus salvage induction, pretransplant chemo-sensitive disease ($p < 0.0001$), and achievement of CR posttransplant were important factors. Important predictors for patients in Groups B and C included low serum albumin ($p < 0.02$) and achievement of CR posttransplant ($p < 0.002$) (Supplementary Table S4, Supplementary Figure S1).

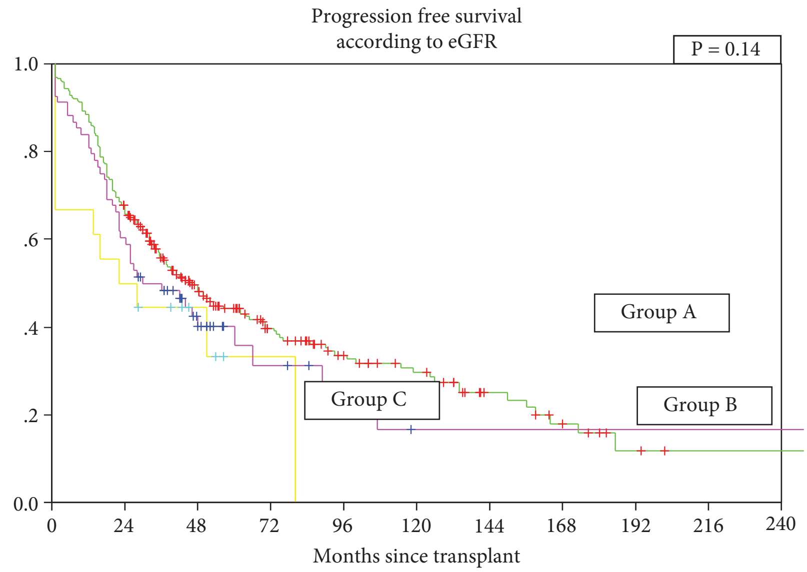

Figure 2 Group A: Patients with normal renal functions (estimation of glomerular filtration rate [eGFR] ≥40 mL/mt) at diagnosis and at transplant, $n = 263$, Group B: Patients with eGFR <40 mL/mt at diagnosis and ≥40 mL/mt prior to transplant, $n = 68$, Group C: Patients with eGFR <40 mL/mt at diagnosis and prior to transplant, $n = 18$.

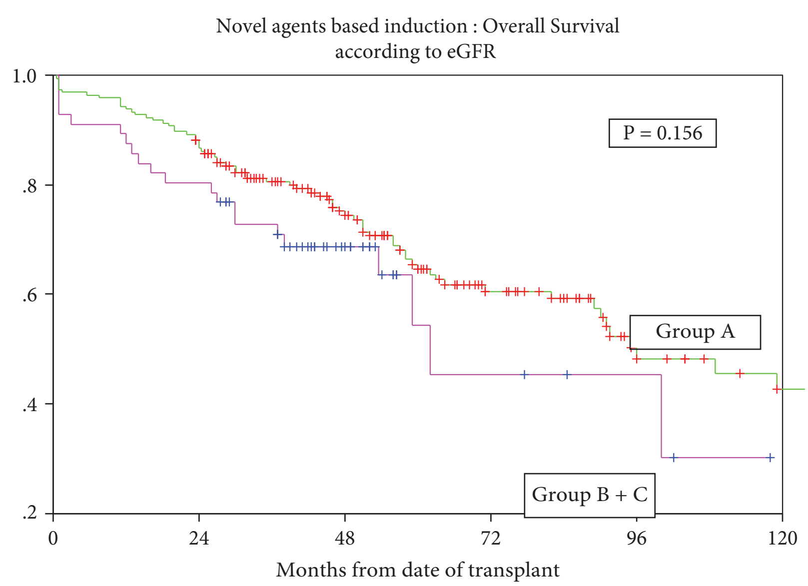

Figure 3 Overall survival for patients who received novel agents-based induction with or without renal impairment.

5.2. Predictors of PFS: Univariate Analysis

For patients in Group A, presence of extramedullary disease ($p < 0.05$), low serum albumin <3.5 g/dL ($p = 0.006$), more than one induction regimen ($p < 0.003$), primary versus salvage induction, pretransplant status ($p < 0.0001$), and achievement of CR posttransplant ($p < 0.0001$) were important predictors. For patients in Groups B and C more than one-line induction treatment, and achievement of CR posttransplant were important predictors of PFS (Supplementary Table S5, Supplementary Figure S2).

5.3. Multivariate Analysis

Independent predictors of OS included ISS stage I + II ($p < 0.02$), absence of extramedullary disease ($p < 0.01$), and achievement of

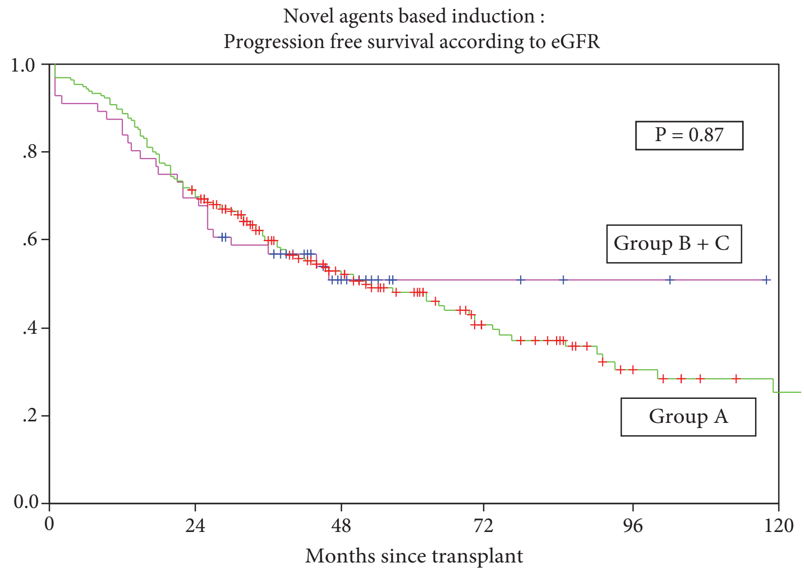

Figure 4 Progression-free survival for patients treated with novel agents with or without renal impairment.

CR posttransplant ($p < 0.001$). For PFS, serum albumin >3.5 g/dL ($p < 0.02$) and achievement of CR posttransplant ($p < 0.001$) were significant predictors (Supplementary Table S6).

6. DISCUSSION

In the present study we have used eGFR <40 mL/min as a cut-off for RI, similar to an earlier study from the Mayo Clinic which showed an optimal cutoff to identify patients with RI [6]. Almost 25% of patients had RI at diagnosis, slightly higher than 22.4% based on serum creatinine >2 mg/dL. This suggests that MDRD remains a useful tool in RI associated with myeloma and is a reasonable equation for the calculation of eGFR in our study population. ISS III myeloma is driven mainly by RI, with 82% of patients having a serum creatinine of more than 2 mg/dL [27] and hence RI in a way is reflective of a higher burden of myeloma and advanced disease. In addition to stage (ISS III, DSS IIIB), other parameters such as serum calcium >11.5 mg/dL, lower median Hb (g/dL), lower serum albumin <3.5 g/dL, and light chain myeloma were overrepresented among patients with RI (Groups B + C) (Table 1). These findings suggest that RI in MM is associated with higher disease burden.

In this study, 79% of patients on induction with novel agents had reversal of renal dysfunction. This is consistent with earlier observations. Several studies have shown that treatment with novel agents leads to a better depth of response and thus higher rates of improvement in renal function [7–9,28–30]. Among these, bortezomib plus thalidomide is renally safe. Bortezomib, in addition to its anti-myeloma effect, has a protective effect on renal tubular cells, and an inhibitory effect on the pro-inflammatory and fibrotic pathways within the renal microenvironment [5,25].

In the present study, a CR to transplant was higher among those who received novel-agent based induction compared with those who received VAD (68.1% versus 48% $p < 0.02$), and in those who received novel agent-based induction compared with those receiving alkylating agents (68.1% versus 26.1%, $p < 0.001$). The overall response rate to transplant was higher for patients in Group A (eGFR >40 mL/min) compared to those in Groups B + C; 93.5% versus 82.5%, $p < 0.003$. But among patients who received novel agent-based induction, we did not observe a difference in response rate (≥PR) among patients (Group A versus Groups B + C) (Supplementary Table S3). These findings suggest that novel agent-based induction can overcome the adverse impact of RI with regard to transplant response.

Engraftment kinetics was generally similar in the two groups (Group A versus Groups B + C) except that patients with RI received a higher number of packed red cells ($p < 0.002$) and single donor platelets ($p < 0.007$) (Table 2). This is similar to earlier observations [17–19,21,29]. Oral mucositis is the main dose limiting toxicity of high-dose melphalan conditioning. Overall mucositis was higher among patients with RI (Groups B + C) compared to those in Group A, 80.2% versus 62.2% $p < 0.01$, this higher risk of oral mucositis in RI patients has been found in earlier studies [17–19,30–32].

In the present study, transplant-related mortality (TRM) at day +100 was 5.2%. Mortality was higher among patients with RI (Groups B + C) compared to Group A: 9/86 (10.5%) versus 9/263 (3.4%), $p < 0.01$. For patients who received novel agent-based induction, TRM was 3.1% (Group A) versus 7.1% (Groups B + C). Other predictors of TRM included low serum albumin ($p < 0.005$), transplant post salvage for relapse ($p < 0.05$), and year of transplant, the TRM being higher in initial years compared to recently ($p < 0.02$) (Table 4). A higher TRM has been reported in earlier studies ranging from 50% in dialysis-dependent severe RI (Knudson *et al.*) [15,33], to 29% (San Miguel *et al.*) [12], 18.5% (Bird *et al.*) [13], 15% (St Bernard *et al.*) [17], 14% (Gertz *et al.*) [16], 12% (Lee *et al.*) [14], 2.6% (Badros *et al.*) [34], and 0% in a recent Center for International Blood and Marrow Transplant Research study [35]. A lower TRM in recent years is possibly due to the use of novel agents for induction leading to better depth of response thereby improving performance status at the time of transplant and also to better supportive care. Higher mortality in patients with moderate to severe RI has been attributed to higher doses of melphalan (e.g.,

Table 4 | Predictors of transplant-related mortality.

Factor	N	Day 100 Mortality (n)(%)	p Value
Age			
≤52 Y	177	11 (6.2)	0.254
>52 Y	172	7 (4.1)	
Gender			
M	236	9 (3.8)	0.08
F	113	9 (8.0)	
ISS ($N = 343$)			
I	103	2 (1.9)	0.229
II	121	7 (5.8)	
III	119	8 (6.7)	
DSS $N = 348$			
≤IIIA	263	9 (3.4)	0.01
IIIB	85	9 (10.6)	
EMD			
Yes	80	5 (6.3)	0.39
No	269	13 (4.8)	
Induction therapy			
Novel agents	251	10 (4.0)	0.13
VAD	75	5 (6.7)	
Alkylating agents	23	3 (13.0)	
No of regimens			
One line	223	8 (3.6)	0.06
>one line	125	10 (8.0)	
Myeloma type $N = 342$			
IgG	204	15 (7.4)	0.09
IgA	57	2 (3.5)	
K + L	81	1 (1.2)	
Interval			
≤12 months	220	10 (4.54)	0.33
>12 months	129	8 (6.2)	
CD34 + (× 10(6)/kg) ($N = 311$)			
0–2.0	76	5 (6.6)	0.292
≥2.1	235	10 (4.3)	
Hb			
≤10 G/dL	201	14 (7.0)	0.05
>10 G/dL	148	04 (2.7)	
S albumin			
<3.5 G/dL	140	13 (9.3)	0.005
≥3.5 G/dL	209	05 (2.4)	
BM plasma cell% $N = 348$			
≤40%	180	10 (5.6)	0.46
>40%	168	8 (4.8)	
Base line eGFR			
≤40 mL/mt	86	9 (10.5)	0.01
>40 mL/mt	263	9 (3.4)	
Serum calcium $N = 324$			
≥11.5 mg/dL	28	3 (10.7)	0.13
<11.5 mg/dL	296	12 (4.1)	
Pre-transplant status			
Sensitive	291	13 (4.5)	0.16
Resistant	58	5 (8.6)	
Melphalan dose $N = 347$			
≤140 mg/m^2	35	2 (5.7)	0.56
>140 mg/m^2	312	16 (5.1)	
Line of treatment			
Primary	245	9 (3.67)	0.05
Relapse-salvage	104	9 (8.65)	
Year of transplant			
Till 2005	81	9 (11.1)	0.02
2006–2010	80	3 (3.8)	
2011–2016	188	6 (3.2)	

200 mg/m^2) [14–18,28,29]. As per the IMWG recommendation [5] we used melphalan at 140–160 mg/m^2 among patients with an eGFR <40 mL/min pretransplant. Perhaps a pharmacokinetic guided dose of melphalan tailored to the individual patient may be a rational way to optimize the dose of melphalan [36].

In our study, the median OS was significantly superior for patients in group A, compared to those with RI (Groups B + C). This observation is similar to those of recent studies [29,35,37] and confirms that novel agent-based induction can overcome the adverse impact of RI on survival. Some of the known prognostic factors, for example, ISS stage I + II, serum albumin (>3.5 g/dL), pretransplant chemosensitive disease, treatment with novel agents, and achievement of CR posttransplant were also predictive of improved outcome in our study.

Lack of renal biopsy data in patients with RI (eGFR <40 mL/min) is an important limitation in our study. It is not clear if the comorbidities, for example, hypertension and diabetes mellitus in several patients, may have contributed to RI. Hypertension was significantly more evident in 33.7% (29/86) of patients with RI compared to 21.7% (57/263) in those in Group B (with eGFR ≥40 mL/min), $p < 0.01$). A further limitation is the lack of cytogenetic/FISH data, precluding its impact on outcome in relation to renal function.

In conclusion, our pragmatic study confirms that for MM patients with RI, novel agent-based induction is associated with significant response rates and reversal of RI in the majority of patients. Consolidation with high-dose chemotherapy and autologous stem cell transplant is safe and overcomes the adverse impact of RI on survival.

CONFLICT OF INTEREST

None declared.

AUTHORS' CONTRIBUTIONS

L.K. Designed the study, analyzed the data, and wrote the manuscript; S.K.C. and R.D. Clinical management, collected the data, helped in analysis and discussion; A.V., S.P. and A.S. Clinical management; A.M. Data collection; R.S. Clinical management, and reviewed the manuscript; P.S.M. Helped in care of patients and analysis; A.S. Helped in care of patients and supervision; R.G. and O.S. Performed myeloma studies; A.B. Clinical management; R.K. and S.T. Imaging; S.M. Pathology and investigations.

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REFERENCES

[1] Durie, BG, Salmon, SE. A clinical staging system for multiple myeloma: correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. Cancer 1975;36;842–54.

[2] Brighten, S, Mateos, MV, Zweegman, S, Larocca, A, Falcone, AP, Oriol, A, *et al.* Age and organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435 individual patient data from 4 randomized trials. Haematologica 2013;98;980–7.
[3] Alexanian, R, Barlogie, B, Dixon, D. Renal failure in multiple myeloma. Arch Intern Med 1990;150;1693–5.
[4] Levey, AS, Stevens, LA, Schmid, CH, Zhang, YL, Castro 3rd, AF, Feldman, HI, *et al.* A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150;604–12.
[5] Dimopoulos, MA, Sonneveld, P, Leung, N, Merlini, G, Ludwig, H, Kastritis, E, *et al.* International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. J Clin Oncol 2016;34;1544–57.
[6] Gonsalves, WI, Leung, N, Rajkumar, SV, Dispenzieri, A, Lacy, MQ, Hayman, SR, *et al.* Improvement in renal function and its impact on survival in patients with newly diagnosed multiple myeloma. Blood Cancer J 2015;5;e296.
[7] Kastritis, E, Anagnostopoulos, A, Roussou, M, Gika, D, Matsouka, C, Barmparousi, D, *et al.* Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica 2007;92;546–9.
[8] Roussou, M, Kastritis, E, Christoulas, D, Migkou, M, Gavriatopoulou, M, Grapsa, I, *et al.* Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents. Leuk Res 2010;34;1395–7.
[9] Dimopoulos, MA, Delimpasi, S, Katodritou, E, Vassou, A, Kyrtsonis, MC, Repousis, P, *et al.* Significant improvement in the survival of patients with multiple myeloma presenting with severe renal impairment after the introduction of novel agents. Ann Oncol 2014;25;195–200.
[10] Dimopoulos, MA, Cheung, MC, Roussel, M, Liu, T, Gamberi, B, Kolb, B, *et al.* Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. Haematologica 2016;101; 363–70.
[11] Chakraborty, R, Muchtar, E, Kumar, S, Buadi, FK, Dingli, D, Dispenzieri, A. The impact of induction regimen on transplant outcome in newly diagnosed multiple myeloma in the era of novel agents. Bone Marrow Transplant 2017;52;34–40.
[12] San Miguel, JF, Lahuerta, JJ, García-Sanz, R, Alegre, A, Bladé, J, Martinez, R, *et al.* Are myeloma patients with renal failure candidates for autologous stem cell transplantation? Hematol J 2000; 1;28–36.
[13] Bird, JM, Fuge, R, Sirohi, B, Apperley, JF, Hunter, A, Snowden, J, *et al.* British society of blood and marrow transplantation. The clinical outcome and toxicity of high-dose chemotherapy and autologous stem cell transplantation in patients with myeloma or amyloid and severe renal impairment: a British society of blood and marrow transplantation study. Br J Haematol 2006;134; 385–90.
[14] Lee, CK, Zangari, M, Barlogie, B, Fassas, A, van Rhee, F, Thertulien, R, *et al.* Dialysis-dependent renal failure in patients with myeloma can be reversed by high-dose myeloablative therapy and autotransplant. Bone Marrow Transplant 2004;33; 823–8.
[15] Knudsen, LM, Nielsen, B, Gimsing, P, Geisler, C. Autologous stem cell transplantation in multiple myeloma: outcome in patients with renal failure. Eur J Haematol 2005;75;27–33.
[16] Gertz, MA, Lacy, MQ, Dispenzieri, A, Hayman, SR, Kumar, S, Leung, N, Gastineau, DA. Impact of age and serum creatinine value on outcome after autologous blood stem cell transplantation for patients with multiple myeloma. Bone Marrow Transplant 2007;39;605–11.
[17] St Bernard, R, Chodirker, L, Masih-Khan, E, Jiang, H, Franke, N, Kukreti, V, Tiedemann, R, Trudel, S, Reece, D, Chen, CI. Efficacy, toxicity and mortality of autologous SCT in multiple myeloma patients with dialysis-dependent renal failure. Bone Marrow Transplant 2015;50;95–9.
[18] Khan, R, Apewokin, S, Grazziutti, M, Yaccoby, S, Epstein, J, van Rhee, F, *et al.* Renal insufficiency retains adverse prognostic implications despite renal function improvement following total therapy for newly diagnosed multiple myeloma. Leukemia 2015;29;1195–201.
[19] Sweiss, K, Patel, S, Culos, K, Oh, A, Rondelli, D, Patel, P. Melphalan 200 in patients with renal impairment is associated with increased short-term toxicity but improved response and longer treatment-free survival. Bone Marrow Transplant 2016;51; 1337–41.
[20] Waszczuk-Gajda, A, Lewandowski, Z, Drozd-Sokołowska, J, Boguradzki, P, Dybko, J, Wróbel, T, *et al.* Autologous peripheral blood stem cell transplantation in dialysis-dependent multiple myeloma patients-DAUTOS study of the Polish Myeloma Study Group. Eur J Haematol 2018;101;475–85.
[21] Augeul-Meunier, K, Chretien, ML, Stoppa, AM, Karlin, L, Benboubker, L, Diaz, JMT, *et al.* Extending autologous transplantation as first line therapy in multiple myeloma patients with severe renal impairment: a retrospective study by the SFGM-TC. Bone Marrow Transplant 2018;53;749–55.
[22] MDRD GFR Equation. https://www.mdcalc.com/mdrd-gfr-equation (accessed May 31, 2019).
[23] Kumar, L, Boya, RR, Pai, R, Harish, P, Mookerjee, A, Sainath, B, *et al.* Autologous stem cell transplantation for multiple myeloma: long-term results. Natl Med J India 2016;29;192–9.
[24] Bladé, J, Samson, D, Reece, D, *et al.* Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102;1115–23.
[25] Ludwig, H, Adam, Z, Hajek, R, Greil, R, Tathova, E, Keil, F, *et al.* light chain induced acute renal failure can be reversed by bortezomib, doxorubicin and dexamethasone in multiple myeloma. Results of a phase II study. J Clin Oncol 2010;28; 4635–41.
[26] Bhowmik, D, Yadav, S, Kumar, L, Agarwal, S, Agarwal, SK, Gupta, S. Sequential autologous hematopoietic stem cell transplant followed by renal transplant in multiple myeloma. Ind J nephrology 2017;27;324–6.
[27] Greipp, PR, San Miguel, J, Durie, BG, Crowley, JJ, Barlogie, B, Bladé, J, *et al.* International staging system for multiple myeloma. J Clin Oncology 2005;23;3412–20.
[28] Yadav, P, Cook, M, Cockwell, P. Current trends of renal impairment in multiple myeloma. Kidney Dis 2015;1;241–57.
[29] Antlanger, M, Dust, T, Reiter, T, Böhm, A, Lamm, WW, Gornicec, M, *et al.* Impact of renal impairment on outcomes after autologous stem cell transplantation in multiple myeloma: a multi-center, retrospective cohort study. BMC Cancer 2018; 18;1008.

[30] Glavey, SV, Gertz, MA, Dispenzieri, A, Kumar, S, Buadi, F, Lacy, M. Long-term outcome of patients with multiple myeloma-related advanced renal failure following auto-SCT. Bone Marrow Transplant 2013;48;1543–7.
[31] Tamaki, M, Nakasone, H, Gomyo, A, Hayakawa, J, Akahoshi, Y, Harada, N, *et al.* Lower glomerular filtration rate predicts increased hepatic and mucosal toxicity in myeloma patients treated with high-dose melphalan. Int J Hematol 2018;108;423–31.
[32] Grazziutti, ML, Dong, L, Miceli, MH, Krishna, SG, Kiwan, E, Syed, N, *et al.* Oral mucositis in myeloma patients undergoing melphalan-based autologous stem cell transplantation: incidence, risk factors and a severity predictive model. Bone Marrow Transplant 2006;38;501–6.
[33] Knudsen, LM, Hjorth, M, Hippe, E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. Eur J Haematol 2000;65;175–81.
[34] Badros, A, Barlogie, B, Siegel, E, Roberts, J, Langmaid, C, Zangari, M, *et al.* Results of autologous stem cell transplant in multiple myeloma patients with renal failure. Br J Haematol 2001; 114;822–9.
[35] Mahindra, A, Hari, P, Fraser, R, Fei, M, Huang, J, Berdeja, J, *et al.* Autologous hematopoietic cell transplantation for multiple myeloma patients with renal insufficiency: a center for international blood and marrow transplant research analysis. Bone Marrow Transplant 2017;52;1616–22.
[36] Shaw, PJ, Nath, CE, Lazarus, HM. Not too little, not too much-just right! (Better ways to give high dose melphalan). Bone Marrow Transplant 2014;49;1457–65.
[37] Scheid, C, Sonneveld, P, Schmidt-Wolf, IG, van der Holt, B, el Jarari, L, Bertsch, U, *et al.* Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial. Haematologica 2014;99;148–54.

SUPPLEMENTARY TABLES AND FIGURES

Table S1 Factors predictive of reversibility of renal functions.

Factor	Group B *N* = 68	Group C *N* = 18	*p* Value
Age			
≤52	33	11	0.247
>52	35	07	
Gender			
Male	43	8	0.121
Female	25	10	
ISS Stage			
I	2	1	0.173
II	11	0	
III	55	17	
DS stage			
≤IIIA	6	0	0.233
IIIB	62	18	
MM type			
IgG	29	9	0.575
IgA	15	2	
K + L	20	6	
EM disease			
Yes	15	3	0.446
No	33	15	
Hb (G/dL)			
≤10	59	16	0.585
>10	09	02	
Albumin (G/dL)			
<3.5	38	11	0.451
≤3.5	30	07	
BM plasma cells			
≤40%	32	8	0.528
>40%	36	10	
S. calcium (mg/dL)			
<11.5	50	9	0.111
≤11.5	13	6	
S. creatinine (mg/dL)			
≤3.0	41	5	0.014
>3.0	27	13	
24-hour urine protein			
<2G	22	3	0.232
≤2G	19	6	
Induction therapy			
Novel agents	47	9	0.298
VAD	13	5	
Alkylating agents	8	4	
No of regimens			
One line	41	8	0.173
>one line	27	10	
Interval			
<12 months	38	9	0.427
≤12 months	30	9	
Pre-transplant status			
CR + VGPR + PR	61	14	0.169
Stable + Prog dis	7	4	
Melphalan dose			
<140 mg/m^2	9	8	0.006
≤140 mg/m^2	59	10	
Response to transplant			
CR + VGPR + PR	59	12	0.05
Stable + Prog dis + died	9	06	

DS = Durie salmon stage; EM = extra-medullary disease; CR = complete response; VGPR = very good partial response; PR = partial response; Prog dis = progressive disease.

Table S2 Pretransplant renal response (status) versus posttransplant myeloma response.

Pretransplant Renal Response Status		Posttransplant Myeloma Response				
	No of Patients	CR (%)	VGPR	Partial	Stable	Died (%)
CR	32	21 (65.6)	7	2	1	1 (3.1)
PR	16	9 (56.3)	3	2	1	1 (6.25)
Minor	21	10 (47.6)	2	1	1	7 (33.3)
No response	12	5 (41.6)	1	3	1	2 (16.6)
Total	81	45 (55.6)	13 (16.04%)	8 (9.9%)	4 (4.9%)	11 (13.58)

Renal CR = eGFR, ≥60 l/mt, Renal partial response-eGFR = 30–59 mL/mt, Renal Minor response = eGFR 15–29 mL/mt (Ref).

Table S3 Response to transplant for patients who received novel agents-based induction ($N = 251$).

Response	All Patients, $N = 251$ (%)	Group A, $N = 195$ (%)	Group B and C, $N = 56$ (%)	p Value
CR	171 (68.1)	131 (67.2)	40 (71.4)	
VGPR	39 (15.5)	32 (16.4)	7 (12.5)	
PR	23 (9.2)	19 (9.7)	4 (7.1)	
Overall CR + VGPR + PR	233 (92.8)	182 (93.3)	51 (91.1)	0.539
Stable	8 (3.2)	7 (3.6)	1 (1.8)	
Died	10 (4.0)	6 (3.1)	4 (7.1)	

Group A: patients who had normal renal functions (eGFR ≥40 mL/mt) at diagnosis and at transplant, Group B: Patients who had RI at diagnosis (eGFR <40 mL/mt), this reversed to ≥40 mL/mt after induction therapy prior to transplant, Group C: patients who had RI at diagnosis and continued to have eGFR <40 mL/mt prior to transplant.

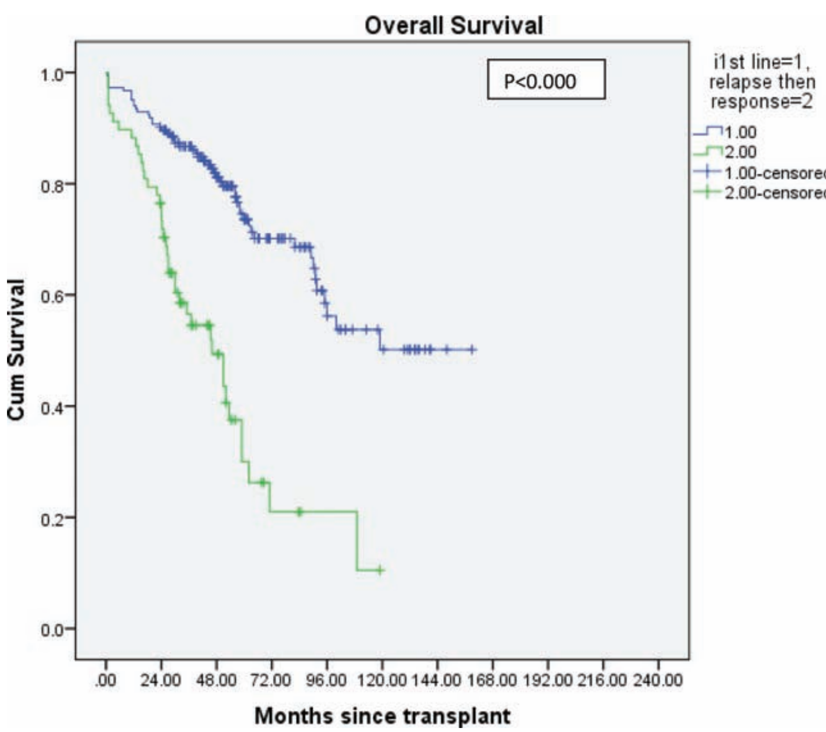

Figure S1 Overall survival for patients who received novel agents: Primary ($n = 183$) versus post salvage ($n = 68$) induction. Blue line indicates patients who underwent transplant after first line induction. Green line indicates patients who had relapsed and received salvage re-induction therapy followed by transplant.

Table S4 | Predictors of overall survival: Univariate analysis.

Factor	No of Pts	Group A, N = 263			Group B, N = 68			Group C, N = 18		
		Median OS (mon)	95% CI	p Value	Median OS (mon)	95% CI	p Value	Median OS	95% CI	p Value
Age in years										
≤52		95.0	50.5	0.53–139.5	103.0	49.9–156.1	0.13	16.0	-	0.94
>52		109.0	75.3–142.7		72.0	25.5–118.5		59.0	25.4–92.6	
Gender										
M	185	109	79.3–138.8	0.21	71.50	54.8–88.2	0.37	59.0	0–142.7	0.34
F	78	89	52.9–125.1		100.0	16.8–183.2		16.0	0–57.8	
ISS										
I	100	127	73.3–180.8	0.02	-	-		28.0	-	0.43
II	110	96.0	61.1–130.9		71.50	2.5–140.5	0.23	-	-	
III	47	52.0	0–105.2		72.0	48.8–95.2		59.0	1.3–116.7	
DSS										
≤IIIA	257	102	75.7–128.3	0.23	72.0	0–185.7	0.94	-	-	-
IIIB	05	73	0–149.4		71.50	44.8–98.2		37.0	5.0–69.0	
EMD										
Yes	62	63.0	30.3–95.7	0.001	30.0	20.0–40.0	0.10	16.0	0–40.0	0.05
No	201	114.5	89.5–139.5		100.0	60.9–139.1		59.0	17.3–100.6	
Albu min (G/dL)										
≤3.5	91	85.0	52.8–117.2	0.0001	59.0	13.2–104.8	0.02	37.0	0–91.6	0.31
>3.5	172	119.0	73.5–164.5		100.0	53.3–146.5		131.0	-	
Hb (G/dL)										
≤10	126	102	55.3–148.7	0.073	72.0	51.192.9	0.76	28.0	0–66.4	0.35
>10	137	97	61.7–132.3		103.0	0–217.3		60.5	-	
BM PC%										
≤40	140	125.5	78.9–172.1	0.50	72.0	55.6–88.4	0.42	59.0	26.3–91.7	0.30
>40	122	89.0	62.2–115.8		79.0	19.1–139.0		16.0	0–57.8	
Ig Type										
IgG	166	102.0	74.4–129.6	0.62	71.5	19.0–124.0	0.58	1.0	-	0.08
IgA	40	90.0	33.5–146.5		79.0	47.1–110.9		60.50	-	
K + L	55	57.2	43.9–268.1		106.0	55.6–156.4		59.0	12.6–105.4	
Induction										
Novel	195	96.0	72.8–119.2	0.009	62.0	50.5–73.5	0.45	-	-	0.05
VAD	57	124.5	73.8–115.2		71.5	8.1–134.9		59.0	0–125.6	
Alky.	11	32.0	12.6–57.4		23.0	0–147.0		1.0	-	
Regimen										
One	174	150	100.7–199.3	0.0001	100.0	47.7–152.3	0.02	60.5	-	0.12
>one	88	54.0	41.7–66.3		37.0	0–84.5		1.0	-	
Pre-Tx status										
Sensiti	216	119.0	87.0–151.0	0.0001	71.50	46.4–96.6	0.92	59.0	3.8–114.2	0.02
resista	47	48.0	29.7–66.3		106.0	0–220.1		1.0	-	
Interval Diag-Tx										
≤12 mo	173	124.50	84.2–164.8	0.011	79.0	34.9–123.1	0.32	59.0	0–166.2	0.19
>12 mo	90	63.0	47.7–78.3		53.5	0.4–106.6		28.0	0–63.1	
Post-Tx response										
CR	163	156.0	105.8–206.2	0.0001	112.0	61.0–163.0	0.002	60.5	58.1–62.9	0.0002
others	83	52.0	41.2–62.8		37.0	0–97.1		28.0	8.8–47.2	

ISS = International staging system; DSS = Durie Salmon staging; Tx = transplant; PC = plasma cell; others = light chain, EMD = extra-medullary disease; sens = sensitive (CR + VGPR + PR); Resis = stable + progressive disease.

Table S5 Predictors of progression-free survival: Univariate analysis.

		Group A			Group B			Group C		
Factor	**Variable**	**Median OS (mon)**	**95% CI**	***p* Value**	**Median OS (mon)**	**95% CI**	***p* Value**	**Median OS**	**95% CI**	***p* Value**
Age in years	≤52	38.0	28.1–47.9	0.65	48.0	12.4–83.6	0.30	13.5	-	0.7
	>52	56.50	32.5–80.5		26.0	16.8–35.2		28.0	12.6–43.4	7
Gender	M	50.0	35.2–64.8	0.14	28.0	3.4–52.6	0.28	51.0	-	0.3
	F	37.0	16.9–57.2		44.0	-		13.50	0–36.7	6
ISS	I	53.0	17.8–88.2	0.07	89.0	-	0.56	16.0	-	0.42
	II	46.0	33.6–58.4		22.0	0–47.9		-	-	
	III	34.0	15.8–52.2		30.0	14.9–45.1		28.0	2.7–65.8	
DSS	≤IIIA	48.0	36.8–59.2	0.17	18.0	0–37.2	0.60	-	-	
	IIIB	29.0	5.4–52.6		36.0	19.4–52.6		22.0	0–47.0	
EMD	Yes	35.0	16.4–53.6	0.05	18.0	4.8–31.3	0.10	13.5	0–33.5	0.05
	No	50.0	33.1–66.9		44.0	23.3–64.7		51.0	8.2–93.8	
Albumin	≤3.5	34.0	20.2–47.8	0.00	22.0	14.5–29.6	0.14	22.0	0–51.13.8	0.3
(G/dL)	<3.5	53.0	30.7–75.3	6	44.0	8.8–79.2		80.0	-	0
Hb	≤10	37.0	25.3–48.7	0.14	36.0	15.8–56.2	0.79	16.0	0.45–32.6	0.5
(G/dL)	>10	51.0	28.9–73.1		22.0	8.9–35.2		51.0	-	3
BM PC%	≤40	65.0	29.4–100.6	0.20	48.0	18.4–77.6	0.27	28.0	0–60.2	0.2
	>40	37.0	27.8–47.2		26.0	18.6–33.3		13.50	0–36.7	7
Ig	IgG	51.0	27.4–74.6	0.61	26.0	17.3–34.8	0.37	1.0	-	0.31
Type	IgA	41.0	25.1–56.9		42	12.3–71.7		51.0	-	
	K + L	42.0	23.9–60.1		30	0–61.5		22.0	0–60.4	
Induction	Novel	52.0	36.3–67.7	0.12	46.0	-	0.02	-	-	0.05
	VAD	36.0	22.3–49.7		20.0	13.0–27.1		22.0	9.1–34.9	
	Alkylatingagent	20.0	13.5–26.5		18.0	6.2–29.8		1.0	-	
Regimen line	One >one	62.0	44.1–80.0	0.0003	60	-	0.0001	51.0	-	0.04
		24.0	12.3–35.7		21	15.9–26.1		1.0	-	
Pre- Tx	Sensiti	62.0	45.5–78.6	0.0001	42.0	20.4–63.6	0.31	51.0	0–114.1	0.0
status	resista	18.0	11.3–24.7		20.0	14.8–25.1		1.0	-	3
Interval	≤12 mo	48.0	32.2–63.8	0.19	42.0	14.6–69.4	0.21	51.0	0–108.5	0.52
Diag-Tx	>12 mo	34.0	17.3–50.7		26.0	8.6–43.4		16.0	8.7–23.3	
Post-Tx	CR	90.0	56.4–123.6	0.0001	66.0	26.2–105.8	0.0001	80.0	-	0.001
response	others	18.0	15.3–20.7		20.0	13.8–26.2		16.0	12.0–20.0	

Table S6 Multivariate analysis.

Variable	*p* Value	Hazard	95% CI
Overall Survival			
Extramedullary disease	0.014	1.684	1.13–2.549
Stage ISS I + II vs III	0.02	0.581	0.361–0.935
Posttransplant CR	0.001	0.352	0.236–0.526
Progression-free survival			
Serum Albumin	0.026	1.535	1.053–2.238
Posttransplant CR	0.001	0.245	0.180–0.334

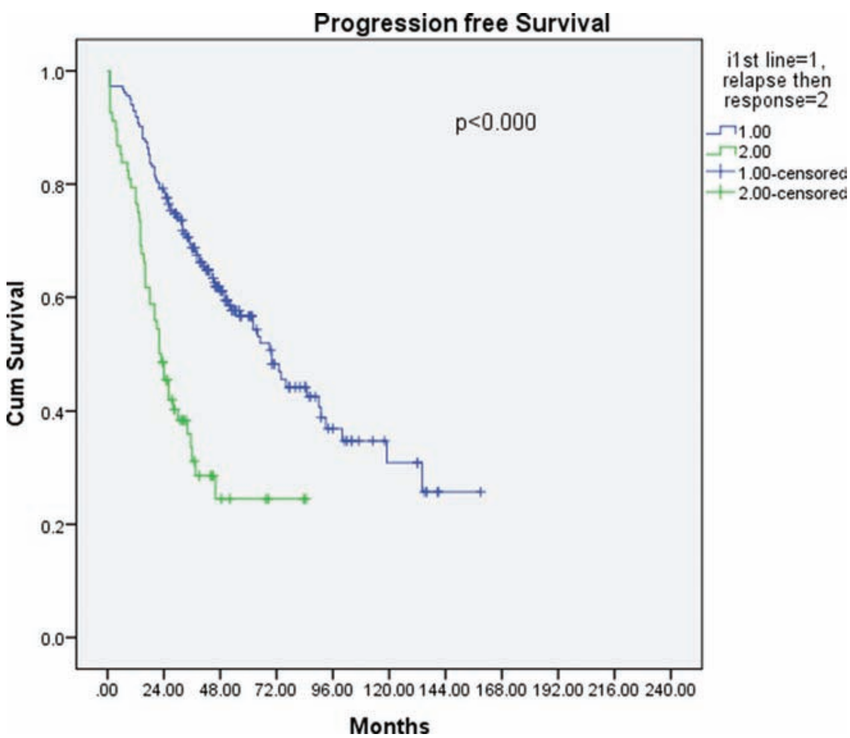

Figure S2 Progression-free survival for patients who received novel agents: Primary versus post salvage induction.