Renal Impairment at Diagnosis in Myeloma: Patient Characteristics, Treatment, and Impact on Outcomes. Results From the Australia and New Zealand Myeloma and Related Diseases Registry

P. Joy Ho,[1] Elizabeth M. Moore,[2] Zoe K. McQuilten,[2] Cameron Wellard,[2] Krystal Bergin,[3] Bradley Augustson,[4] Hilary Blacklock,[5] Simon J. Harrison,[6] Noemi Horvath,[7] Tracy King,[1,8] Peter Mollee,[9] Hang Quach,[10] Christopher Reid,[2] Brian Rosengarten,[11] Patricia Walker,[3] Erica M. Wood,[2] Andrew Spencer[3]

Abstract

Renal impairment (RI) is common in patients with multiple myeloma (MM) and is associated with poor prognosis. The Australia and New Zealand Myeloma Registry was used to assess >1000 newly diagnosed MM patients, of whom 383 had RI at diagnosis. Patients who underwent autologous stem cell transplantation (ASCT) despite RI had improved survival; potential factors for an inferior outcome include suboptimal use of bortezomib and ASCT.

Background: Renal impairment (RI) is a common complication of multiple myeloma (MM) and remains a poor prognostic factor despite improved survival with newer therapies. **Patients and Methods:** We evaluated baseline characteristics, treatment, and outcomes of newly diagnosed MM patients with RI at diagnosis in the Australia and New Zealand Myeloma and Related Diseases Registry over 5 years to April 2018; we compared patients with RI (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) with those with eGFR ≥ 60. In autologous stem cell transplantation (ASCT) analyses, patients aged 70 years and younger and ≥ 1 year from diagnosis were included. **Results:** Overall, 36% of patients with newly diagnosed MM had RI; they were older, had more advanced disease and comorbidities, and worse performance status. Bortezomib-based induction therapy was most commonly used, although administered to fewer RI patients, despite similar response rates. Patients with RI were less likely to receive ASCT; however, recipients had longer progression-free survival (PFS) and overall survival (OS). Patients with RI had shorter OS and PFS after adjusting for age. In ASCT recipients with RI versus no RI, there was no difference in PFS and OS. **Conclusion:** Our findings in "real world" MM patients with RI confirm that patient-, disease-, and treatment-related factors (such as suboptimal bortezomib and ASCT use), and delays in commencing therapy, might contribute to poorer outcomes, and support the use of ASCT in patients with RI.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 19, No. 8, e415-24 © 2019 Elsevier Inc. All rights reserved.
Keywords: Autologous, Multiple myeloma, Registry, Renal Impairment, Transplantation

[1]Institute of Haematology, Royal Prince Alfred Hospital, Missenden Road, Camperdown, New South Wales, and University of Sydney, Sydney, Australia
[2]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[3]Department of Haematology, Alfred Health-Monash University, Melbourne, Victoria, Australia
[4]Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia
[5]Middlemore Hospital, Middlemore, Auckland, New Zealand
[6]Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Peter MacCallum Department of Oncology, University of Melbourne, Parkville, Melbourne, Australia
[7]Royal Adelaide Hospital, Adelaide, South Australia, Australia
[8]Sydney Nursing School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia
[9]Haematology Department, Princess Alexandra Hospital, Woolloongabba, Queensland, School of Medicine, University of Queensland, Brisbane, Australia
[10]University of Melbourne, St Vincent's Hospital, Victoria, Australia
[11]Myeloma Australia, Richmond, Victoria, Australia

Submitted: Jan 28, 2019; Revised: Apr 14, 2019; Accepted: May 12, 2019; Epub: May 16, 2019

Address for correspondence: P. Joy Ho, MBBS, Institute of Haematology, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, NSW 2050, Australia
E-mail contact: joy.ho@sydney.edu.au

2152-2650/$ - see frontmatter © 2019 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.clml.2019.05.010

Introduction

Renal impairment (RI) is a poor prognostic factor in patients with multiple myeloma (MM). Despite improvements in survival with the introduction of novel therapies in recent years, RI remains one of the most common complications with an incidence of 20% to 50% at diagnosis, and approximately 5% to 10% of MM patients are dialysis-dependent.[1-3] The most common cause of RI in MM is cast nephropathy, in which excess light chains form aggregates and casts resulting in tubular blockage and inflammation.[4-6] Other factors include toxic effects of light chains on the basement membranes of glomeruli and proximal tubules, interstitial nephritis, amyloid deposition, and plasma cell infiltration, which are further exacerbated by hypercalcemia, dehydration, hyperuricemia, and nephrotoxic drugs. Patients with myeloma also present with RI from other causes and it is important to determine their outcomes.

Recent developments including the significant efficacy of proteasome inhibitor (PI) use in reversing renal failure, and the development of other new agents (such as monoclonal antibodies) are likely to improve disease outcome. The role of autologous stem cell transplantation (ASCT) in the transplantation-eligible (TE) population with RI has not been definitively established. Current International Myeloma Working Group (IMWG) guidelines indicate level C evidence for ASCT at a reduced melphalan conditioning dose of 140 mg/m^2; however some studies have shown the feasibility and efficacy of full-dose conditioning,[7,8] despite others recommending dose reduction in some patients.[7,9] The choice of induction agent(s) in TE and non-TE patients also varies, and whether combination therapy provides incremental benefit in this high-risk group needs further clarification.

With the overall improvement in prognosis in MM patients,[10] it is crucial to evaluate whether there has been comparable progress in outcomes for this high-risk group with RI. In Australia and New Zealand, treatment protocols usually follow government reimbursement policy, for which combination novel therapies and maintenance therapy (other than thalidomide) are as yet unavailable outside of clinical trials. We investigated current treatment and clinical outcomes for MM patients with RI at diagnosis in Australia and New Zealand using a large, binational, real world, prospective clinical registry.

Patients and Methods

Data Sources

Data for this study were obtained from the Australian and New Zealand Myeloma and Related Diseases Registry (ANZ MRDR). Details regarding the methods of the MRDR have been published separately,[11] and it is registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12618000659202). In brief, the MRDR is a prospective registry established in 2012, of newly diagnosed patients aged 18 years and older with MM, monoclonal gammopathy of undetermined significance (MGUS), smoldering MM, plasma cell leukemia, or solitary plasmacytoma identified by participating sites. The MRDR uses an opt-out consent model. Patient characteristics, comorbidities, disease characteristics, laboratory parameters, and first-line therapy data are collected at baseline; then data on therapy, response, disease progression, and other outcomes are collected every 4 months for MM patients and annually for MGUS patients. Periodic linkage is performed with the national death registries in Australia and New Zealand to ensure the quality of survival/mortality outcomes and to provide supplementary data on date and cause of death for any patients lost to follow-up.

Patients

For this analysis we included all patients with newly diagnosed MM registered in the ANZ MRDR from February 1, 2013 to April 24, 2018.

Definitions

The Kidney Disease: Improving Global Outcomes (KDIGO) classification for chronic kidney disease[12] was used to classify renal function as recommended by the IMWG.[6] The estimated glomerular filtration rate (eGFR) reported in the registry is generally derived from laboratory results using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which has been recommended for use in Australasian laboratories since 2012.[13] RI was defined as eGFR <60 mL/min/1.73 m^2. We adopted this criterion as according to the KDIGO system, the categories ≥90 mL/min/1.73 m^2 and 60 to 89 mL/min/1.73 m^2 denote normal and mildly decreased renal function, respectively, whereas categories <60 mL/min/1.73 m^2 define a more than mild reduction in eGFR. Patient-, disease-, and treatment-related factors were compared. Standard IMWG criteria for response were used.[14]

We classified TE patients as those aged 70 years or younger at diagnosis; the analyses only included patients with a diagnosis date ≥1 year before data extraction (to allow time for transplantation) and who had follow-up data.

Statistical Analysis

Summary statistics are presented as proportion, mean (standard deviation) or median (interquartile range [IQR]) as appropriate. Comparisons between groups were made using the χ^2, Wilcoxon rank sum, or Kruskal–Wallis test as appropriate. Overall survival (OS) and progression-free survival (PFS) were calculated using Kaplan–Meier survival analysis, with censoring on death. The proportional hazards assumption was tested and all analyses were done using Stata version 15.1 (StataCorp LLC, College Station, TX).

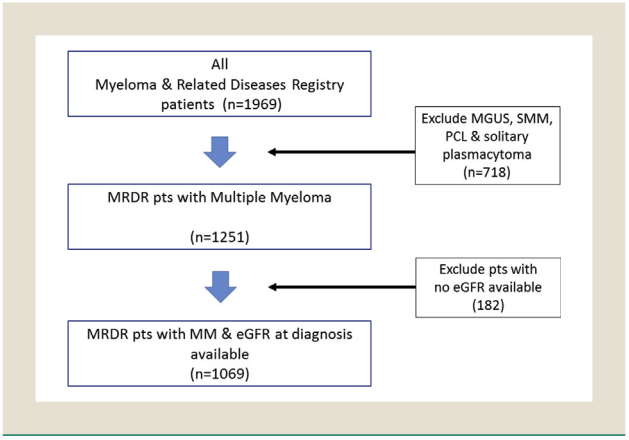
Results

Patient and Disease Characteristics

Of 1251 patients with MM in the MRDR, 1069 (85%) had eGFR available at diagnosis (Figure 1), and these 1069 patients were used in the RI analyses. Of these patients, 36% had RI (eGFR <60 mL/min/1.73 m^2), 24% had eGFR 30 to 59 mL/min/1.73 m^2, 6% had eGFR 15-29 mL/min/1.73 m^2, and eGFR was <15 mL/min/1.73 m^2 in 6% of patients.

Compared with patients who had normal renal function, patients with RI at diagnosis were older (72 vs. 65 years; $P < .001$) and had more advanced stage disease according to the International Staging System (ISS) of III: 66% versus 13%; Revised-ISS (R-ISS) III: 34% versus 5%; $P < .001$; Table 1). RI can affect ISS stage (ISS and R-ISS) because β-2 microglobulin is affected by renal function, we reviewed the other staging criteria to determine whether RI alone was the reason for increased stage in this group. The R-ISS components of high-risk fluorescence in situ hybridization (FISH) and

Figure 1 Patient Flow Chart



Abbreviations: eGFR = estimated glomerular filtration rate; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MRDR = Myeloma and Related Diseases Registry; PCL = plasma cell leukemia; pts = patients; SMM = smoldering multiple myeloma.

lactate dehydrogenase (LDH) analysis were compared, and showed that 57% with RI versus 44% with no RI had these high-risk changes ($P = .01$). Patients with RI had a higher LDH (205 U/L; 164-261 U/L) compared with no RI (186 U/L; 152-234 U/L; $P < .001$), which is likely to reflect myeloma cell proliferation. High-risk FISH abnormalities were present in 31% of patients with RI, and 24% with no RI ($P = .07$).

Patients with RI had a worse performance status (Eastern Cooperative Oncology Group [ECOG] performance status of 2-4: 30% vs. 18%; $P < .001$) and more comorbidities; more patients with RI had diabetes (15% vs. 9%; $P = .005$), cardiac disease (15% vs. 8%; $P < .001$), and abnormal liver function tests (2.6% vs. 0.7%; $P = .01$). There was no difference in the prevalence of pulmonary disease or peripheral neuropathy between the 2 groups (Table 1).

In disease manifestations other than RI defining MM activity, hypercalcemia (10% vs. 4%; $P = .001$) and anemia (43% vs. 16%; $P < .001$) were both more common in patients with RI; however fewer patients with RI had bone lesions (53% vs. 67%; $P < .001$).

Treatment and Response

The time from diagnosis to commencement of induction therapy was shorter in patients with RI (median 15 days; IQR, 13-18 days; 90th centile, 60 days) compared with no RI (25 days; IQR, 22-27; $P < .001$). Bortezomib-based therapy was most commonly used for induction in all patients, however it was given to fewer patients with RI (80% vs. 88%; $P = .002$; Table 2). Carfilzomib-based therapy was used in 2.2% of patients with RI and 0.5% of non-RI patients. Overall the percentage of patients who received a PI of either bortezomib or carfilzomib was still lower in patients with RI (82.5%) compared with non-RI (88.3%; $P = .013$). Although carfilzomib is not approved for first-line treatment of MM in our jurisdiction, a clinical trial on carfilzomib/dexamethasone was in progress specifically for RI patients during the period of data collection. Contrary to the understanding that PIs are particularly effective in MM patients with RI, there was no obvious factor identified for the lower proportion of RI patients receiving a PI as first-line therapy compared with other treatments. We investigated the possibility that parenteral treatment of bortezomib might be less favored in older patients compared with oral treatment, but this was not the case because a greater proportion of patients with RI older than 70 years compared with no RI received bortezomib (75% [145/193] vs. 69% [120/173]), with the reverse finding in patients 70 years or younger (86% [143/166] vs. 94% [448/475]). Response rates (partial response or better [≥PR]) to bortezomib in both groups were similar (≥PR rate 81% in RI vs. 84% in no RI; $P = .28$), and there was also no statistically significant difference in response to thalidomide-based therapy between groups (≥PR: RI 48% vs. no RI 67%; $P = .12$).

Fewer TE patients (defined in Patients and Methods) with RI received ASCT (62% vs. 78%; $P < .001$) and ASCTs were performed in patients at all levels of renal function including in patients with severe RI (eGFR <30 mL/min/1.73 m^2). The proportion of patients who received transplantation at each eGFR level was: eGFR 30 to 59 mL/min/1.73 m^2, 63%; eGFR 15 to 30 mL/min/1.73 m^2, 58%; and eGFR <15 mL/min/1.73 m^2, 61%. Standard-dose melphalan (200 mg/m^2) was given for ASCT conditioning in 72% versus 93% of patients with RI versus no RI, and lower-dose melphalan (140 mg/m^2) in 27% versus 5% of RI versus no RI (Table 2). Among patients who were younger than 70 years and had >1 year follow-up, those who received ASCT compared with those who did not receive ASCT, were younger (59.8 years vs. 65.0 years; $P < .001$), had better performance status, a higher median eGFR (81 vs. 68 mL/min/1.73 m^2; $P < .001$); but there was no significant difference in R-ISS categories (see Supplemental Table 1 in the online version).

Although the age of 70 years is commonly accepted within our jurisdiction as a threshold for transplantation eligibility, we specifically reviewed the age group 65 to 70 years to determine whether patients in this group closest to the threshold were less likely to receive an ASCT if they had RI. For patients with and without RI, a lower proportion of older patients between 65 and 70 years received transplantation compared with patients younger than 65 years; the difference appeared to be more pronounced in the RI group (RI: 44% vs. 71%; no RI: 61% vs. 85%).

Of 383 patients with RI at diagnosis, 18 received dialysis close to diagnosis, however, 2 received dialysis for medical problems unrelated to myeloma. Of the remaining 16 patients, 94% (15/16) had eGFR <15 mL/min/1.73 m^2 at diagnosis, and 88% (14/16) received bortezomib first-line chemotherapy, with ≥PR of 75% (9/12). Only 38% (3/8) versus 64% (87/137) of patients who received dialysis versus those who did not receive dialysis underwent ASCT ($P = .14$), however, there was no statistically significant difference in treatment, response, OS, or PFS between groups ($P \geq .06$), which might be because of a lack of power because of the low numbers. Of the patients who received dialysis, 7/16 (44%) became dialysis-independent within 3 months of commencement.

Plasma exchange was administered in 1.0% of patients with RI versus 1.7% in those with no RI ($P = .36$).

Progression-Free and Overall Survival

Median patient follow-up was 19 months. PFS and OS were reduced in patients with RI: median PFS was 25 versus 33 months ($P < .001$), and median OS 47 months for RI, versus not reached; $P < .001$ (Table 2). For patients with RI, 75% were alive at 23

Table 1 Patient Characteristics at Diagnosis (eGFR <60 vs. eGFR ≥60 mL/min/1.73m^2)

	eGFR <60 mL/min/1.73 m^2	eGFR ≥60 mL/min/1.73 m^2	*P*
n	383	686	—
Serum Creatinine, μmol/L	143.0 (113.0-229.0)	76.0 (67.0-88.0)	<.001
eGFR	39.0 (21.0-51.0)	83.0 (71.0-90.0)	<.001
Paraprotein Type			
IgG	202/379 (53.3)	415/679 (61.1)	
IgA	70/379 (18.5)	142/679 (20.9)	
IgM	2/379 (0.5)	3/679 (0.4)	
IgD	6/379 (1.6)	3/679 (0.4)	
Light chain κ	61/379 (16.1)	68/679 (10.0)	
Light chain λ	35/379 (9.2)	31/679 (4.6)	
Nonsecretory MM	2/379 (0.5)	12/679 (1.8)	
Biclonal	1/379 (0.3)	5/679 (0.7)	
Light Chain Isotype			.85
κ	173/275 (62.9)	349/549 (63.6)	
λ	102/275 (37.1)	200/549 (36.4)	
Age, Years	71.6 (63.2-79.1)	64.5 (56.5-71.0)	<.001
Age >70 Years	212/383 (55.4)	188/686 (27.4)	<.001
Male Sex	233/383 (60.8)	421/685 (61.5)	.84
ISS = 3	191/289 (66.1)	64/513 (12.5)	<.001
R-ISS = 3	62/181 (34.3)	18/351 (5.1)	<.001
β2 Microglobulin, mg/L	6.9 (4.6-12.2)	3.0 (2.3-4.1)	<.001
Albumin, g/L	33 (28-37)	35 (31-40)	<.001
High-Risk Group (FISH or LDH)[a]	79/138 (57.2)	126/284 (44.4)	.01
High-Risk FISH[b]	50/160 (31.3)	82/346 (23.7)	.07
LDH, U/L[c]	205.0 (164.0-261.0)	186.0 (152.0-234.0)	<.001
LDH ≥300	32/234 (13.7)	51/485 (10.5)	.21
ECOG Performance Status = 2-4	74/249 (29.7)	84/467 (18.0)	<.001
Diabetes[d]	56/383 (14.6)	62/686 (9.0)	.005
Moderate to Severe Cardiac Disease	59/383 (15.4)	57/686 (8.3)	<.001
Moderate to Severe Pulmonary Disease	25/383 (6.5)	31/686 (4.5)	.16
Abnormal Liver Function Tests	10/383 (2.6)	5/686 (0.7)	.01
Peripheral Neuropathy	14/383 (3.7)	14/686 (2.0)	.11
Hypercalcemia	40/383 (10.4)	30/686 (4.4)	<.001
Anemia	163/383 (42.6)	108/686 (15.7)	<.001
Bone Lesions	202/383 (52.7)	456/686 (66.5)	<.001

Data are presented as median (IQR) or n (%).
Abbreviations: ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; FISH = fluorescence in situ hybridization; IQR = interquartile range; ISS = International Staging System; LDH = lactate dehydrogenase; MM = multiple myeloma; R-ISS = Revised International Staging System.
[a]High risk group = patients with high-risk FISH analysis results; abnormalities: del17p, t(4;14), t(14;16), amp(1q21), or high LDH ≥300.
[b]FISH abnormalities: del17p, t(4;14), t(14;16), amp1q21.
[c]Upper limit of normal for LDH = 250 U/L.
[d]Diabetes requiring medication.

months (18-27 months) versus 38 months (35-43 months) for no RI (Figure 2). After adjustment for age, the hazard ratios (HRs) for OS and PFS were 0.62 (95% confidence interval [CI], 0.47-0.81; $P < .001$) and 0.74 (95% CI, 0.61-0.91; $P = .004$), respectively. After adjustment for other comorbidities—moderate to severe cardiac disease and ECOG performance status—in addition to age, the HRs for OS and PFS were 0.72 (95% CI, 0.52-0.99; $P = .045$) and 0.80 (95% CI, 0.63-1.03; $P = .087$), respectively.

Progression-free and OS were compared across all stages of chronic kidney disease and are illustrated in Figure 2C and D, indicating a decreasing trend in survival time with reduced renal function.

In patients with RI who received bortezomib versus thalidomide-based first-line chemotherapy (n = 285 vs. 32, those who received both [n = 3] were excluded) there was no difference in PFS (HR, 0.78; 95% CI, 0.48-1.27; $P = .32$) or OS (HR, 0.89; 95% CI, 0.49-1.61; $P = .70$).

Table 2 Treatment, Response, and Survival (eGFR <60 vs. eGFR ≥60 mL/min/1.73 m^2)

	eGFR <60 mL/min/1.73 m^2	eGFR ≥60 mL/min/1.73 m^2	*P*
N	383	686	
Time From Dx to Rx, Days	15.0 (13.0-18.0)	25.0 (22.0-27.0)	<.001
Time From Dx to ASCT, Days	199 (155-279)	195 (165-249)	.55
Overall Best Clinical Response (≥PR)	219/272 (80.5)	457/547 (83.5)	.28
Bortezomib-Based Therapy	288/359 (80.2)	568/648 (87.7)	.002
BCR in Bortezomib-Based Therapy (≥PR)	194/228 (85.1)	423/492 (86.0)	.75
Thalidomide-Based Therapy	35/359 (9.7)	54/648 (8.3)	.45
BCR in Thalidomide-Based Therapy (≥PR)	11/23 (47.8)	31/46 (67.4)	.12
Lenalidomide-Based Therapy	11/359 (3.1)	16/648 (2.5)	.58
BCR in Lenalidomide-Based Therapy (≥PR)	2/5 (40.0)	7/9 (77.8)	.16
Carfilzomib-Based Therapy	8/359 (2.2)	4/648 (0.5)	.02
BCR in Carfilzomib-Based Therapy (≥PR)	6/6 (100)	1/1 (100)	
Bortezomib or Carfilzomib-Based Therapy	296/359 (82.5)	571/648 (88.1)	.01
ASCT Performed and Age ≤70 Years[a]	90/145 (62.1)	335/429 (78.1)	<.001
ASCT Conditioning			<.001
Melphalan 200 mg/m^2	70/97 (72.2)	341/365 (93.4)	
Melphalan 140 mg/m^2	26/97 (26.8)	17/365 (4.7)	
Other[b]	1/97 (1.0)	7/365 (1.9)	
Plasma Exchange Therapy Used	4/383 (1.0)	12/686 (1.7)	.36
Median PFS (95% CI), Months	24.9 (21.3-28.5)	33.1 (29.7-36.4)	<.001
Overall Survival (95% CI), Months	47.2 (41.9-50.4)	67.1 (58.8+)	<.001
Cause of Death: Disease-Related (MM)	61/70 (87)	69/81 (85)	.73
Deceased Patients	119 (31.1)	118 (17.2)	
Chemotherapy Regimens Administered in Deceased Patients	1.5 (1-3)	2 (1-3)	.08

Data are presented as median (IQR) or n (%) except where otherwise noted.
All chemotherapy drug and response variables relate to first-line therapy.
Abbreviations: ASCT = autologous stem cell transplantation; BCR = best clinical response; Dx = diagnosis; eGFR = estimated glomerular filtration rate; MM = multiple myeloma; PFS = progression-free survival; ≥PR = partial response or better to therapy; Rx = therapy.
[a]Patients with diagnosis date ≥1 year before data extraction and with follow-up data (age ≤70 is used because this is consensus practice for transplantation eligibility in Australia and New Zealand and only 10 patients aged >70 years had ASCT).
[b]Alternative doses of melphalan or other conditioning used.

Transplantation-eligible patients with RI who received ASCT had a longer OS (HR, 0.41; 95% CI, 0.19-0.90; $P = .03$) and PFS (HR, 0.54; 95% CI, 0.32-0.93; $P = .03$) compared with those who did not receive an ASCT (Figure 3).

In ASCT recipients, there was no difference in PFS (HR, 0.97; 95% CI, 0.62-1.50; $P = .87$) or OS (HR, 0.82; 95% CI, 0.41-1.62; $P = .57$) between patients with and without RI (Figure 4).

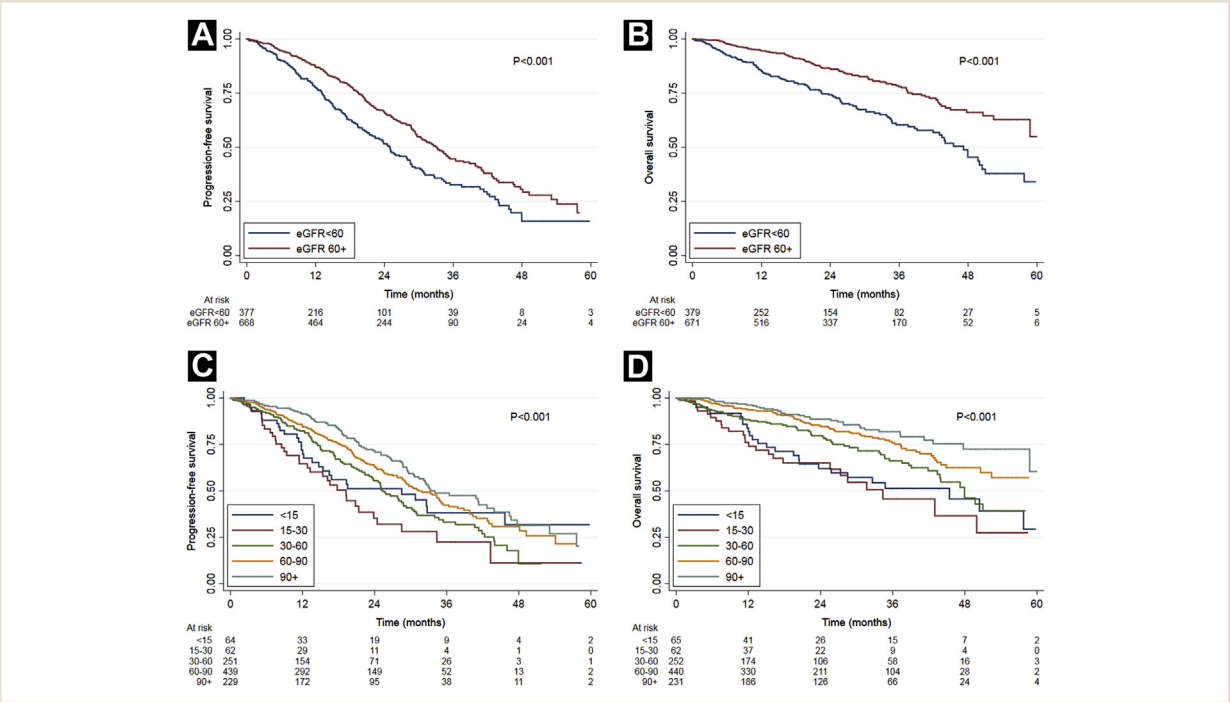
Patients with RI who received melphalan 200 mg/m^2 had a shorter median PFS than those who received 140 mg/m^2 (31 months vs. not reached; $P = .05$; HR, 0.43; 95% CI, 0.18-1.04; $P = .06$), however, there was no significant difference in OS or response to therapy (≥PR) between groups.

Of 491 patients who were aged 70 years or younger and received an ASCT, only 201 patients had data available on maintenance therapy. Of these patients 151/201 (75.1%) received thalidomide, the only agent approved for maintenance in our jurisdiction: 93 (46.2%) received thalidomide alone, 58 (28.9%) received thalidomide with prednisolone, 5 (2.5%) received prednisolone alone. Other maintenance therapies including bortezomib, lenalidomide and panobinostat were administered in the remaining 45 patients, of whom most (33/45 [73%] or 33/201 [16%] of the total cohort with maintenance data) was administered in clinical trials.

Overall, 119 patients have died in the RI group (31%) and 118 patients in the no-RI group (17%). There was no significant difference in the median number of chemotherapy regimens administered before death.

Because diabetes is the most important cause of RI in the Australian population,[15] we evaluated the possible effect of diabetes requiring treatment on myeloma outcome. We found no effect on PFS, OS, or response to first-line therapy ($P \geq .8$). Although a larger proportion of patients with RI had diabetes than no RI (Table 1), in patients with RI, there was no significant difference in outcome between those with and without diabetes (≥PR, 80.5% versus 80.6%; $P = .99$; PFS, 25.0 [95% CI, 19.5-34.4] versus 24.5 [95% CI, 20.2-28.5] months; $P = .89$; OS, 38.7 [30.2 to not reached] versus 47.9 [95% CI, 43.4-57.8] months; $P = .80$]. In the Australian community the 2 other major causes of renal failure are glomerulonephritis and hypertension, for which current data in our registry do not enable an accurate assessment of their effect.

Figure 2 Progression-Free and Overall Survival in Multiple Myeloma According to Renal Function at Diagnosis. (A) and (B) Show a Comparison of eGFR <60 Versus ≥60 mL/min/1.73 m^2; (C) and (D) Show a Comparison of eGFR Categories for Chronic Kidney Disease



Abbreviation: eGFR = estimated glomerular filtration rate.

Discussion

Key Findings

In our analysis of 1069 newly diagnosed MM patients from the ANZ MRDR, we found 36% had RI at diagnosis and this was associated with older age, presence of comorbidities, worse performance status, and higher-risk disease. Bortezomib-based therapy was the most common first-line treatment in patients with RI, although this was used less frequently compared with those without RI, despite similar response rates. Patients with RI had a shorter OS and PFS compared with patients without RI after adjusting for age. In keeping with this finding, an overall trend for a shorter PFS and OS was observed with a reduction in eGFR. Patients with RI were less likely to receive an ASCT; however those with RI who received transplantation had a longer PFS and OS than those who did not. In addition, OS and PFS were similar in those who received ASCT irrespective of the presence of RI.

It is clear from previous studies that in the overall MM population, PFS and OS are superior for TE compared with non-TE patients.[16] In our study, the improved PFS and OS for patients with no RI compared with RI remained significant after adjustment for age. However, because age, comorbidities, and performance status all constitute important eligibility criteria for ASCT, it is not surprising that when PFS and OS were adjusted for all of these factors, the differences between RI and no RI became less pronounced, as this adjustment would mitigate the effect of ASCT on prognosis.

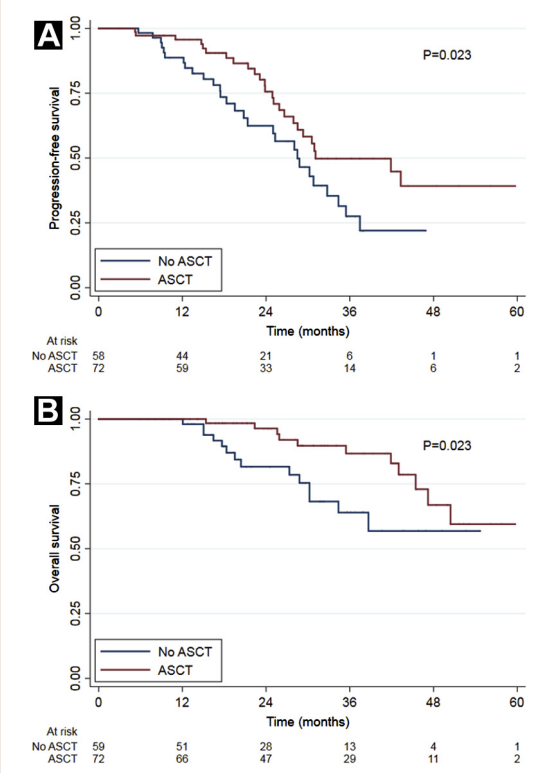
In clinical trials of novel drugs or regimens in MM, patients with RI are often excluded, which limits our understanding of their response to treatment and outcomes. This cohort is from a binational registry of >1250 myeloma patients with eGFR available from 85% of patients, providing the opportunity for assessment of the incidence, underlying factors, treatment, and outcomes in patients with newly diagnosed MM with RI in a large "real world" population.

Comparison With Other Studies

We showed that patients with RI represented a third of patients with newly diagnosed MM in the MRDR and that RI is associated with a poor prognosis,[17-19] consistent with other findings.[6,20,21] MM patients with RI were older, had a higher prevalence of advanced stage disease, and higher LDH levels (correlated with myeloma cell proliferation, despite a lower prevalence of bone lesions), and shorter PFS and OS.

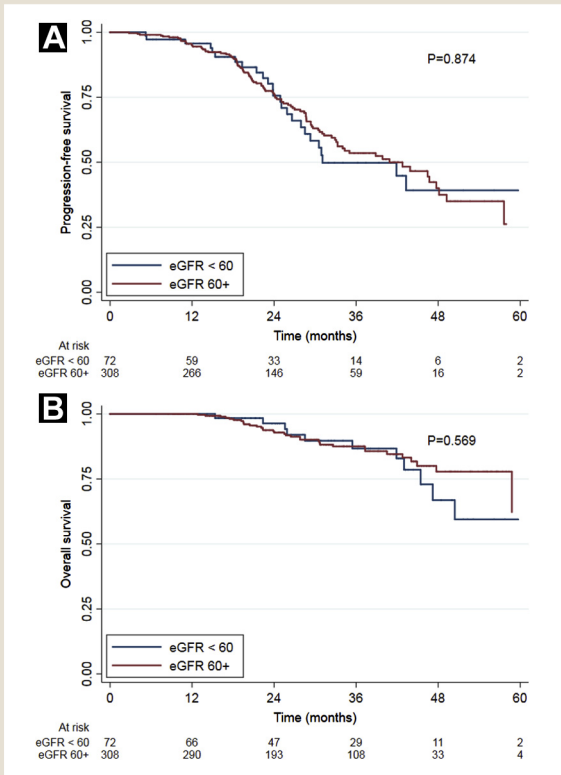
Because it is clear that PI have particular effectiveness in patients with RI and MM,[22] it is of interest to note that fewer RI patients in this population received them compared with the cohort without RI. We investigated the possibility that age might be a factor favoring oral immunomodulator therapy in the older age group but this was not the case. It is also possible that the RI was considered by the treating doctor not to be due to MM in some of these patients, and hence a PI was not used in the initial treatment. Furthermore, there was no difference in the best clinical response between patients

Figure 3 Progression-Free and Overall Survival in Patients With Multiple Myeloma and Renal Impairment (eGFR <60 mL/min/1.73 m^2) at Diagnosis, in Patients Who Had and Did Not Have Autologous Stem Cell Transplantation (ASCT)



Abbreviation: eGFR = estimated glomerular filtration rate.

Figure 4 Progression-Free and Overall Survival in Patients With Multiple Myeloma Who Had Autologous Stem Cell Transplantation, in Patients With eGFR <60 versus ≥60 mL/min/1.73 m^2 at Diagnosis



Abbreviation: eGFR = estimated glomerular filtration rate.

with RI versus no RI either in bortezomib-based or thalidomide-based treatment. In addition, for patients with RI who received bortezomib versus thalidomide-based first-line chemotherapy, there was no significant difference in PFS or OS ($P > .32$), however, the number of patients who received thalidomide was low (n = 32). Before the era of "novel agents," RI in patients with MM was associated with poor prognosis.[23-25] Since then, evidence suggests that the reversal of RI may be associated with an improvement in prognosis[26-28] with novel agents playing a significant role.[10,29] However, because long-term follow-up data on renal response is not routinely collected on all MRDR patients, it was not possible to ascertain the difference in efficacy of each treatment in reversing RI. Given the importance of prompt initiation of treatment in patients with RI, and the established link between reversal of RI and prognosis, it is pleasing to see that the median time from diagnosis to treatment for RI (median 15 days; IQR, 13-18 days) is significantly lower although still considered clinically suboptimal; it is of even greater concern that 10% of RI patients started treatment after 60 days.

This study has shown that ASCT is commonly performed in Australian and New Zealand patients with RI and at all levels of renal function, however, the rate of ASCT is still lower in patients with RI than in patients with normal renal function (62% vs. 78%; $P < .001$). This was particularly the case in patients close to the age threshold of transplantation eligibility of 65 to 70 years, for which the difference was 44% versus 71% for RI versus no RI. A long-standing concern is the reported increased morbidity and mortality of ASCT in patients with RI, attributed to the possible accumulation of melphalan, the most common conditioning agent, which requires renal clearance. The evidence for ASCT in MM patients with RI is heterogeneous. A recent Center for International Blood and Marrow Transplant Research (CIBMTR) review[8] showed that for patients who received ASCT no difference was seen in PFS or OS for patients with different levels of renal function. The study did not include a comparison with patients who did not receive transplantation. The same CIBMTR report did not show any difference in outcomes between full-dose (200 mg/m^2) and reduced-dose (140 mg/m^2) conditioning, except in a group with eGFR 30-59 mL/min/1.73 m^2, in whom a higher dose of melphalan (200 mg/m^2) was associated with improved PFS. In contrast, a clinical trial of ASCT in patients with eGFR <30 mL/min/1.73 m^2 showed that only reduced-dose melphalan conditioning of 140 mg/m^2 led to an improved PFS compared with historical controls with normal renal function.[30]

Our study showed that patients with RI who underwent ASCT were more likely to have a longer PFS and OS than those who did not receive ASCT. Furthermore, in patients who underwent ASCT, there was no difference in PFS and OS between patients with and without RI. These results support the use of ASCT in TE patients with RI and with appropriate performance status. However, we found that a significantly lower proportion of patients with RI received ASCT compared with those with no RI. The worse ECOG status of patients with RI (Table 1) may have accounted for TE patients with RI not receiving ASCT. In addition, in our cohort, a significantly higher percentage of patients with RI versus no RI (27% vs. 5%) are treated with the lower melphalan dose (140 mg/m^2). Patients with RI who received melphalan 200 mg/m^2 had a shorter PFS than those who received 140 mg/m^2 (31 months vs. not reached; $P = .05$; HR, 0.43; 95% CI, 0.18-1.04; $P = .06$), however, there was no significant difference in OS or response to therapy (≥PR) between groups. Thus, as in the CIBMTR study, we saw no clear advantage for either of the 2 doses of melphalan conditioning.

At the time of data collection, the only funded maintenance treatment available in our jurisdiction was thalidomide. Of patients 70 years of age or younger who received an ASCT and had data on maintenance therapy (n = 201), three-quarters received thalidomide, and the remainder were given numerous therapies including small numbers treated with bortezomib, lenalidomide, and panobinostat maintenance, predominantly in clinical trials. Because of the lack of maintenance therapy data in more than half of the patients who received transplantation and the heterogeneity of regimens, we cannot compare strategies and their effect on disease; rather we can present an overall view of maintenance therapy use in our community.

Of 383 patients with RI, 16 received dialysis for reasons related to their myeloma disease. There was no significant difference in treatment, response, OS, or PFS between the groups of patients who received dialysis versus those who did not ($P \geq .06$), which might be due to lack of power with the low numbers. However, it was pleasing to see that of the patients who received dialysis, 7/16 (44%) became independent of dialysis within 3 months of commencement.

Although we were not able to determine the cause of shortened OS definitively from the registry data for patients with RI; potential contributing factors include suboptimal use of PIs and ASCT. There was no evidence of increased treatment-related mortality: cause of death was disease-related in 87% of patients with RI and 85% without RI. It is likely that reduced efficacy of treatment leading to earlier relapse in patients with RI (as seen in the shorter PFS) is the main cause of the reduced OS rather than treatment-related or other causes of mortality.

Strengths and Limitations

The use of a binational clinical registry with 5 years of prospective data collection from 23 institutions representing metropolitan and regional health care underlies the strength and generalizability of our findings. Limitations include the observational nature of the study, missing data on baseline renal function in 15% of patients, the lack of data on the precise cause of RI (MM or non-MM related) and the absence of follow-up data for renal function to assess renal outcomes.

Conclusion

These findings confirm the higher risk of MM in the presence of RI at diagnosis, with a shortened PFS and OS. Although patient characteristics such as more advanced age, poorer ECOG status, and higher tumor burden might be important factors, our findings also reveal possible treatment-related factors such as delay in commencing treatment, with 10% of RI patients starting treatment after 60 days, as well as a suboptimal utilization of bortezomib and ASCT as possible contributors. Our findings clearly support the use of ASCT in MM patients with RI to achieve better OS and PFS, with no advantage of either full-dose or reduced-dose melphalan conditioning. Although follow-up data on renal response were not available, just over 40% of patients who received dialysis because of MM became dialysis-independent within 3 months of treatment. With our understanding of the importance of consolidation and maintenance in TE and non-TE patients with normal renal function, future review of these additional strategies will provide useful information. Furthermore, the introduction of induction therapies such as the newer PIs, immunomodulatory drugs, and monoclonal antibodies will also likely change the outlook for this group of high-risk patients.

Clinical Practice Points

- Patients diagnosed with MM frequently have RI (36% of MM in our cohort) which is known to be associated with adverse outcomes.
- In a large real-world MM cohort, this study confirms the adverse prognostic effect of RI on MM patients, and describes the factors that contribute to adverse outcomes.
- Treatment-related factors that may have contributed to adverse outcomes are a prolonged time to induction therapy, and suboptimal utilization of bortezomib and ASCT.
- More than 40% of patients who receive dialysis because of MM at diagnosis became dialysis-independent within 3 months of treatment.
- Results suggest that the increased use of ASCT in appropriate patients, PIs for induction, and a reduction in delay to treatment could lead to improved prognosis in patients with MM and RI.

Acknowledgments

The authors thank the patients, hospitals, clinicians, and research staff at participating institutions for their support of the MRDR. This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors, however, the ANZ MRDR has received funding from Amgen, Bristol-Myers Squibb, Celgene, Gilead, Janssen, Novartis, and Takeda.

Disclosure

P.J.H. reports advisory board membership (unpaid) for Amgen, Celgene, Janssen, Novartis, and Takeda, and meeting costs from Celgene and Takeda outside the submitted work. KB reports nonfinancial support: BMS, and personal fees: Celgene. B.A. reports financial support for attendance at a scientific meeting from Celgene, and advisory board membership for BMS, Celgene, and Janssen. H.B. reports membership of the Myeloma Advisory Board

for Janssen, New Zealand. T.K. reports advisory board membership (unpaid) from Janssen, travel support for scientific meeting attendance from Amgen, and being an invited overseas speaker (unpaid) for Amgen. P.M. reports advisory board membership (unpaid) for Celgene, Janssen, Pfizer, and Amgen, and meeting costs from Celgene. H.Q. reports advisory board membership for Amgen, Celgene, GSK, Karyopharm, and Takeda, drug provision for research from Amgen, Celgene, and Sanofi, and research funding from Amgen and Celgene. A.S. reports advisory board membership for Celgene, Janssen, Servier, Takeda, Haemologix, and Abbvie, and project funding from Janssen, Celgene, and GSK. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

The supplemental table accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2019.05.010.

References

1. Goldschmidt H, Lannert H, Bommer J, Ho AD. Multiple myeloma and renal failure. *Nephrol Dial Transplant* 2000; 15:301-4.
2. Laforet M, Jourde-Chiche N, Haddad F, et al. Evolution in the treatment of multiple myeloma and impact on dialysis independence: data from a French cohort from 1999 to 2014. *Blood Cancer J* 2016; 6:e409.
3. Yadav P, Cook M, Cockwell P. Current trends of renal impairment in multiple myeloma. *Kidney Dis (Basel)* 2016; 1:241-57.
4. Huang ZQ, Sanders PW. Biochemical interaction between Tamm-Horsfall glycoprotein and Ig light chains in the pathogenesis of cast nephropathy. *Lab Invest* 1995; 73:810-7.
5. Sengul S, Zwizinski C, Simon EE, Kapasi A, Singhal PC, Batuman V. Endocytosis of light chains induces cytokines through activation of NF-κB in human proximal tubule cells. *Kidney Int* 2002; 62:1977-88.
6. Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group recommendations for the diagnosis and management of myeloma-related renal impairment. *Clin Oncol* 2016; 34:1544-57.
7. El Fakih R, Fox P, Popat U, et al. Autologous hematopoietic stem cell transplantation in dialysis-dependent myeloma patients. *Clin Lymphoma Myeloma Leuk* 2015; 15:472-6.
8. Mahindra A, Hari P, Fraser R, 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.
9. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. *Lancet* 2009; 374:324-39.
10. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* 2008; 111:2516-20.
11. Bergin K, Moore E, McQuilten Z, et al. Design and development of the Australian and New Zealand (ANZ) myeloma and related diseases registry. *BMC Med Res Methodol* 2016; 16:151-8.
12. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005; 67:2089-100.
13. Johnson DW, Jones GR, Mathew TH, et al. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations. *Med J Aust* 2012; 197:224-5.
14. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; 17:e328-46.
15. Australia and New Zealand Dialysis and Transplant Registry. The 40th Annual ANZDATA Report. Available at: http://www.anzdata.org.au/v1. Accessed: March 30, 2019.
16. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014; 28:1122-8.
17. Knudsen LM, Hippe E, Hjorth M, Holmberg E, Westin J. Renal function in newly diagnosed multiple myeloma–a demographic study of 1353 patients. The Nordic Myeloma Study Group. *Eur J Haematol* 1994; 53:207-12.
18. Brenner H, Gondos A, Pulte D. Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010. *Haematologica* 2009; 94:270-5.
19. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003; 78:21-33.
20. Park S, Han B, Kim K, et al. Renal insufficiency in newly-diagnosed multiple myeloma: analysis according to International Myeloma Working Group consensus statement. *Anticancer Res* 2014; 34:4299-306.
21. Nasr SH, Valeri AM, Sethi S, et al. Clinicopathologic correlations in multiple myeloma: a case series of 190 patients with kidney biopsies. *Am J Kidney Dis* 2012; 59:786-94.
22. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring dialysis. *Am J Hematol* 2016; 91:499-502.
23. Augustson BM, Begum G, Dunn JA, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002–Medical Research Council Adult Leukemia Working Party. *J Clin Oncol* 2005; 23:9219-26.
24. Eleutherakis-Papaiakovou V, Bamias A, Gika D, et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. *Leuk Lymphoma* 2007; 48:337-41.
25. Rayner HC, Haynes AP, Thompson JR, Russell N, Fletcher J. Perspectives in multiple myeloma: survival, prognostic factors and disease complications in a single centre between 1975 and 1988. *Q J Med* 1991; 79:517-25.
26. Blade J, Fernandez-Llama P, Bosch F, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. *Arch Intern Med* 1998; 158:1889-93.
27. 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.
28. Kastritis E, Anagnostopoulos A, Roussou M, 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.
29. Kastritis E, Zervas K, Symeonidis A, et al. Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG). *Leukemia* 2009; 23:1152-7.
30. Augeul-Meunier K, Chretien ML, Stoppa AM, 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.

Supplemental Table 1 Characteristics of Patients Younger Than 70 Years of Age Who Were Diagnosed With MM >1 Year Before Data Extraction and Had Follow-up Data (Defined as TE in This Study), According to ASCT Versus No ASCT

Factor	Level	No ASCT	ASCT	*P*
n		168	491	
Median Age at Diagnosis (IQR)		65.0 (58.7-68.1)	59.8 (53.0-64.4)	<.001
Male Sex, n (%)		100/168 (59.5)	314/490 (64.1)	.29
ISS, n (%)	1	26/110 (23.6)	132/353 (37.4)	.029
	2	50/110 (45.5)	131/353 (37.1)	
	3	34/110 (30.9)	90/353 (25.5)	
R-ISS, n (%)	1	4/80 (5.0)	26/229 (11.4)	.12
	2	61/80 (76.3)	175/229 (76.4)	
	3	15/80 (18.8)	28/229 (12.2)	
ECOG Performance Status, n (%)	0	36/109 (33.0)	138/330 (41.8)	<.001
	1	42/109 (38.5)	146/330 (44.2)	
	2	19/109 (17.4)	36/330 (10.9)	
	3	8/109 (7.3)	10/330 (3.0)	
	4	4/109 (3.7)	0/330 (0.0)	
Median eGFR (IQR)		68 (45-81)	81 (64-90)	<.001

Although more complete data were available for ISS than R-ISS, and there appeared to be a significantly higher number of patients in lower ISS stages within the ASCT group, R-ISS is considered to be more informative because of the greater reliance of ISS on β-2 microglobulin (being 1 of 2 parameters), which can be affected by eGFR. The absence of a difference in R-ISS indicates no significant difference in MM stage in potential TE patients who received or did not receive an ASCT.

Abbreviations: ASCT = autologous stem cell transplantation; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; IQR = interquartile range; ISS = International Staging System; MM = multiple myeloma; R-ISS = Revised International Staging System; TE = transplantation-eligible.