

Real-world prognostic factors in autotransplanted multiple myeloma patients with severe renal impairment: study of the Polish Myeloma Study Group

Anna Waszczuk-Gajda^{1*#}, David H. Vesole², Jolanta Małyszko³, Artur Jurczyszyn^{4#}, Tomasz Wróbel^{5#}, Joanna Drozd-Sokołowska^{1#}, Piotr Boguradzki^{1#}, Krzysztof Mądry^{1#}, Agnieszka Tomaszewska^{1#}, Jarosław Biliński^{1#}, Maria Król^{1#}, Longin Niemczyk⁵, Magdalena Olszewska-Szopa^{5#}, Wiesław W. Jędrzejczak^{1#}, Grzegorz W. Basak^{1#}

¹Department of Haematology, Oncology, and Internal Medicine, Warsaw Medical University, Warsaw, Poland

²Myeloma Division, John Theurer Cancer Centre, Hackensack University Medical Centre, NJ, USA

³Department of Nephrology, Dialysis therapy, and Internal Diseases, Medical University of Warsaw, Warsaw, Poland

⁴Department of Haematology, Jagiellonian University Medical College, Krakow, Poland

⁵Department and Clinic of Haematology, Blood Neoplasms, and Bone Marrow

Transplantation, Wrocław Medical University, Wrocław, Poland

[#]Polish Myeloma Study Group

***Corresponding author:**

Anna Waszczuk-Gajda MD, PhD

Department of Haematology, Oncology, and Internal Medicine
Warsaw Medical University
1a Banacha St
02-097 Warsaw, Poland
Phone: +48 22 599 28 18
Fax: +48 22 599 14 18
E-mail:
anna.waszczuk-gajda@wum.edu.pl

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Abstract

Introduction: The prognostic factors in autotransplanted multiple myeloma (MM) patients with concomitant advanced chronic kidney disease (CKD) are poorly understood, limited, and controversial.

Material and methods: We retrospectively analysed 44 patients with MM and CKD (eGFR < 40 ml/min), present both at diagnosis and at autologous stem cell transplantation (ASCT), with no improvement of renal function in-between.

Results: Patients exhibiting deeper paraprotein responses to pre-transplant treatment predicted better response post ASCT (odds ratio (OR) = 11.6, $p = 0.028$) and longer progression-free survival (PFS) (hazard ratio (HR) = 0.23, $p = 0.017$). Higher albumin concentration (per increase of 1 g/dl) (HR = 0.41, $p = 0.03$) and melphalan 140 mg/m² versus higher melphalan doses (HR = 0.86, $p = 0.008$) were associated with longer PFS. Performance status (ECOG 0-1 versus ≥ 2) (HR = 0.28, $p = 0.0036$), higher albumin concentration (HR = 0.43, $p < 0.037$), and melphalan 140 mg/m² versus higher melphalan doses (HR = 0.48, $p = 0.081$) decreased the risk of death. Three of 32 dialysis-dependent patients became dialysis independent (DID), and 5 of 12 in the DID group had eGFR improvement post ASCT. The median PFS was 2.3 years, which was shorter for DID compared to DD patients (0.7 vs. 3.3 years, respectively). The median overall survival (OS) was 3.6 years, there was no difference in median OS between the groups (4.0 vs. 3.5 years, respectively).

Conclusions: Optimal patient selection including good performance status and higher albumin concentration (with every increase of 1 g/dl), chemotherapy-responsive disease pre-ASCT, melphalan dose adjusted to CKD, and intensive post-transplant supportive care are crucial to achieve acceptable results of treatment of MM patients with CKD.

Key words: multiple myeloma, advanced chronic kidney disease, autologous stem cell transplantation, dialysis.

Introduction

Approximately 25–50% of patients with newly diagnosed multiple myeloma (MM) are diagnosed with renal dysfunction [1, 2]. Successful reversal of renal impairment is multi-faceted and depends on numerous disease and patient characteristics. Renal failure, in general, is associated with shorter survival [3]; however, this is not uniformly true. The aetiology of renal failure in MM patients is multi-factorial, including the direct toxic effect of monoclonal light chains precipitating in the distal collecting renal tubules resulting in tubulointerstitial damage but also dehydration and hypercalcaemia. Moreover, administration of nephrotoxic drugs can also contribute to renal injury. Patients with estimated glomerular filtration rate (eGFR) lower than 30 ml/min are frequently excluded from clinical trials, and consequently only limited data are available on the safety profile in patients with end-stage renal impairment. The data on the pharmacodynamic and toxicity profile of many drugs in patients with chronic kidney disease (CKD) are also lacking.

Although improvement in renal function, including dialysis independence (DID), in dialysis-dependent (DD) MM patients may be observed after first-line treatment, there remains a group of patients who do not demonstrate improvement in renal function. Patients with extremely reduced eGFR are frequently considered ineligible for autologous stem cell transplantation (ASCT) because of a higher risk of treatment-related toxicities, including death. However, in recent years, in several studies it was found that ASCT may be effective and safe in patients with severe renal impairment [4–9]. Moreover, in some studies it was found that severe renal impairment may be partly reversible in a proportion of patients, especially when ASCT is performed early in the course of the disease [10–12].

In this study, we evaluated the prognostic factors for response, progression-free survival (PFS), and overall survival (OS) in MM patients with severe renal impairment (eGFR lower than 40 ml/min), who underwent ASCT.

Material and methods

Patients

The data were analysed of 44 MM patients with advanced CKD at the time of diagnosis and at ASCT (eGFR lower than 40 ml/min), who did not show improvement in renal function between diagnosis and ASCT according to International Myeloma Working Group (IMWG) criteria [13]. We used the common definition of renal impairment in MM as eGFR lower than 40 ml/min or serum creatinine concentration higher than 2 mg/dl [14]. We excluded patients who were dialysis-inde-

pendent at the diagnosis and became DD due to disease progression and those who had an eGFR lower than 40 ml/min at diagnosis and improved to values greater than 40 ml/min prior to ASCT.

eGFR was calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation [15] and the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation [16]. MDRD is considered a more accurate measure of eGFR than CKD-EPI when eGFR is lower [15]. In DID MM patients, assuming that the baseline eGFR was < 50 ml/min/ 1.73 m², renal response was defined according to IMWG 2016 criteria: the complete renal response (rCR) was defined as best improvement of eGFR ≥ 60 ml/min, renal partial response (rPR) as improvement from < 15 ml/min/ 1.73 m² to 30–59 ml/min, and renal minor response (rMR) as improvement from < 15 ml/min to 15–29 ml/min (best eGFR) or from 15–29 ml/min to 30–59 ml/min [13].

All the patients were treated with ASCT between 2004 and 2016 in two Polish transplant centres, and data were collected within the Polish Myeloma Study Group. Records submitted by physicians were evaluated and reviewed for accuracy. The physicians from all over Poland referred eligible patients with dialysis-dependent myeloma to two mentioned centres that have an option of both bone marrow transplantation and nephrology renal replacement therapy in the same institution. The study obtained institutional review board approval of the Medical University of Warsaw for the participating centres.

All the patients had performance status 0–2 according to Eastern Cooperative Oncology Group (ECOG), without significant cardiac, pulmonary, or hepatic dysfunction or active infection. All patients received a high-dose melphalan-containing preparative regimen supported with an infusion of previously collected and cryopreserved autologous peripheral blood stem cells [8]. Melphalan was administered over a 60-minute infusion on day –1 pre ASCT. ASCT was performed on day 0. A minimum of 2.0×10^6 CD34+ cells/kg were infused. Standard posttransplant supportive care was provided.

Statistical analysis

Patients characteristics were summarised using the median and interquartile range (IQR) or numbers and percentages for continuous and categorical variables, respectively. The overall response rate was evaluated according to IMWG Uniform Response Criteria [17]. The primary endpoint was OS, calculated from the time of ASCT to the day of the last follow-up or death. Secondary endpoints were: response after transplant according to IMWG [17], PFS calculated from time of ASCT

to disease progression or death from any cause or the last follow-up, transplant-related mortality (TRM), transplant-related toxicity graded according to Common Toxicity Criteria of Adverse Events 3.0 (CTCAE) [18], and renal improvement according to IMWG [13].

OS and PFS curves were calculated using the Kaplan-Meier method; differences between the subgroups were assessed by log-rank test. Prognostic factors affecting response and PFS/OS after ASCT were evaluated by univariate logistic regression (calculation of odds ratio (OR)) and by univariate Cox's proportional hazards of regression (calculation of hazard ratio (HR)), respectively. Multivariate analysis was not possible to assess due to the low sample size. Results were considered to be statistically significant for $p < 0.05$. All calculations were performed using the SAS version 9.4 software package.

Results

Patients

All the patients had CKD (32 patients required dialysis) both at diagnosis and ASCT and had no improvement of renal function between diagnosis and ASCT (Table I). Twelve patients had severe CKD but were DID. All patients had ISS (International Staging System) 3 MM [19]. Data on cytogenetic risk groups are missing. The median time from diagnosis to ASCT was 280 days (interquartile range (IQR): 197–368). Pre-transplant responses included complete response (CR), very good partial response (VGPR), and partial response (PR) observed in 8 (19%), 9 (21%), and 16 (37%) of the 33 responding patients, respectively. The 11 (25%) remaining patients did not achieve at least PR. Melphalan doses ranged from 100 to 200 mg/m²: 100 mg/m² in 11%,

Table I. Patients' characteristics ($N = 44$) (* $N = 43$)

Characteristics	Number (%) or median (IQR)
At diagnosis:	
Age [years]	56.7 (54.7–59.8)
Age > 60 year	10 (23)
Female gender	23 (52)
Diagnosis before 2012	25 (57)
Haemoglobin concentration [g/dl]	9.0 (8.2–9.8)
Albumin concentration [g/dl]	3.5 (3.1–4.0)
β 2-microglobulin concentration [mg/l]	32.2 (17.0–39.8)
Creatinine concentration [mg/dl]	5.6 (3.7–8.8)
GFR CKD-EPI [ml/min]	8.2 (4.8–13.5)
GFR MDRD [ml/min]	8.8 (5.1–14.3)
Dialysis dependence	32 (73)
Paraprotein type:	
IgG	21 (48)
IgA	4 (9)
IgD	2 (4.5)
Light Chain Lambda	10 (22.5)
Light Chain Kappa	7 (16)
Stage according to Durie-Salmon classification:	
1B	1 (2)
2B	2 (4)
3B	41 (94)
Bone lytic change	44 (100)
Before ASCT:	
General performance status according to WHO:	
0	24 (55)
1	8 (18)
2	12 (27)

Characteristics	Number (%) or median (IQR)
≥ 1 comorbidity	18 (41)
First line chemotherapy regimens:	
Thalidomide-based chemotherapy	21 (48%)
VAD (vincristine, Adriamycin, dexamethasone)	12 (27)
Bortezomib-based chemotherapy	8 (18)
Ctx-Dex (cyclophosphamide, dexamethasone)	2 (4.5)
ASCT front-line	1 (2)
More than one line of induction therapy	13 (30)
Response to induction therapy*:	
CR	8 (19)
VGPR	9 (21)
PR	16 (37)
SD	6 (14)
PD	4 (9)
ORR (CR, VGPR, PR)*	33 (77)
Conditioning regimen: melphalan dose:	
100 mg/m ²	5 (11)
140 mg/m ²	28 (64)
200 mg/m ²	11 (25)
At ASCT:	
Creatinine concentration [mg/dl]	5.1 (2.2–6.7)
eGFR CKD-EPI [ml/min]	10.1 (7.2–28.8)
eGFR MDRD [ml/min]	10.9 (9.0–30.2)

140 mg/m² in 64%, and 200 mg/m² in 25% of the patients (Table I).

Haematological recovery, response, and toxicity

The median time to neutrophil (ANC ≥ 0.5 × 10⁹/l) and platelet engraftment (> 20 × 10⁹/l) without transfusion support was 12 days and 11 days, respectively (Table II). The 30-day TRM was 2%: 1 patient died of sepsis (at 17 days post ASCT) (Table III). Of the 43 patients evaluable for response (response was evaluated 3 months after ASCT), 11 (26%) achieved CR, 8 (19%) VGPR, and 15 (35%) PR (Table II). Three (9%) patients became DID (Table II) (rCR). Of 12 DID multiple myeloma patients with eGFR < 40 ml/min, 3 had GFR improvement fulfilling criteria of renal complete response (rCR), and 2 had partial renal response (pCR).

The median duration of hospital stay was 29 days (IQR: 20–36 days) (Table III). Parenteral nutrition was required by 16 (36%) patients, and 15 (34%) patients were treated with opioids. The most common toxicities (all grades) were mucositis (80%), infections (77%), and diarrhoea (52%) (Table III). Platelet transfusion and red blood cell transfusions were needed in 37 (77%) and 34 (74%) patients, respectively.

Overall survival and progression-free survival

With a median follow-up of 3.4 years (confidence interval (CI): 0.5–12.7), the median PFS was 2.3 years (CI: 0.8–9.7) and median OS was 3.6 years (CI: 0.4–12.7) (Figure 1, Table II). After 5 years, 42% of patients were alive and 32% were progression free (Table II).

Survival outcomes of DD patients and DID patients, with severe renal disease, were compared: the PFS was shorter for DID patients compared to DD patients (0.7 vs. 3.3 years; due to the small sample size no *p*-value was calculated), and there was no difference in median OS between the two groups (4.0 vs. 3.5 years, respectively) (Table III).

Prognostic factors of response and overall survival

Overall response (CR, VGPR, or PR) to induction chemotherapy positively predicted response to ASCT (OR = 11.6, 95% CI: 1.31–103, *p* = 0.028). Better response to pretransplantation treatment according to IMWG criteria was associated with post-ASCT response.

The presence of lambda light chain monoclonal protein was a negative predictor of VGPR or CR after ASCT (OR = 0.1, 95% CI: 0.01–0.82, *p* = 0.032).

Prognostic factors associated with shorter PFS included: presence of proteinuria (HR = 1.14, CI:

1.01–1.27, *p* < 0.029) and cardiac complications (HR = 14.9, CI: 2.46–90.2, *p* < 0.003), need for parenteral nutrition (HR = 2.48, CI 1.10–5.60, *p* > 0.023), and diarrhoea of at least grade 3 (HR = 2.32, CI: 1.01–5.56, *p* < 0.046). Predictors of decreased risk of progression were the following:

Table II. Outcomes of ASCT

Outcome	Results
Time to neutrophil recovery (Neu ≥ 0.5 G/l) [days]*	12 (11–14)
Time to platelet recovery median (PLT ≥ 20G/l) [days]*	11 (9–15)
Response to ASCT*:	
CR	11 (26%)
VGPR	8 (19%)
PR	15 (35%)
SD	3 (7%)
PD	6 (14%)
Patients off dialysis – dialysis independent (N = 32)	3 (7%)
Progression-free survival (PFS):	
Median [years]	2.27
3-year PFS (%)	40
5-year PFS (%)	32
Overall survival (OS):	
Median [years]	3.6
3-year PFS (%)	56
5-year PFS (%)	42

Table III. Toxicities ≥ grade 3 (N = 44)

Toxicity	Number (%) or median (IQR)
Mucositis	20 (46)
Diarrhoea	11 (25)
Gastrointestinal complications	2 (5)
Infections including neutropenic fever/excluding neutropenic fever	33 (75)/20 (43)
Haemorrhagic complications	3 (7)
Neurological complications	3 (7)
30-days TRM	1 (2)
Toxicity management:	
Parenteral nutrition	16 (36)
Usage of opioids	15 (34)
Platelet concentrate transfusion	37 (77)
Number of platelet concentrates transfused [U]	2.5 (1–4)
Patients with red blood cell transfusion (yes vs. no)	34 (74)
Red blood cells transfused [U]	2 (1–4)
Duration of hospitalisation [days]	29 (20–36)

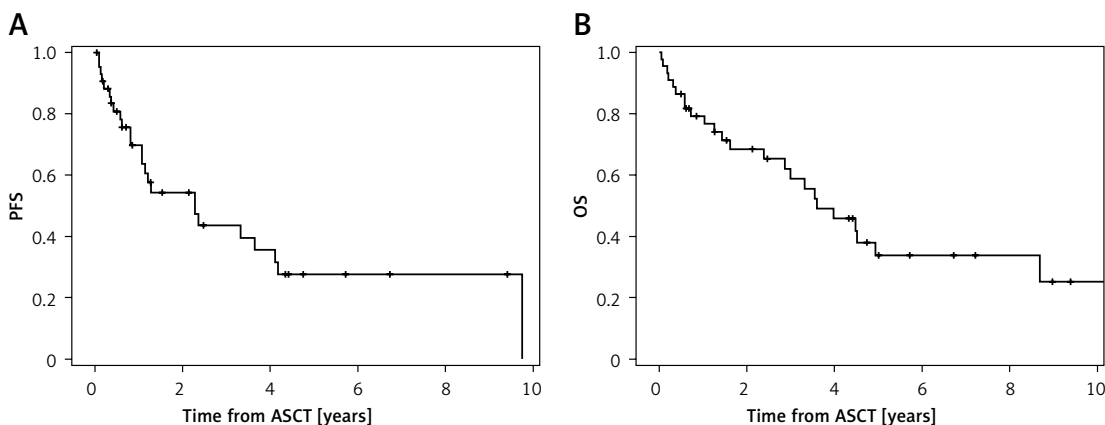


Figure 1. Survival outcomes. **A** – Progression-free survival (PFS), **B** – overall survival (OS)

preserved higher albumin concentration (with every increase per 1 g/dl) (HR = 0.41, CI: 0.18–0.93, $p < 0.03$), melphalan dose of 140 mg/m² versus other (HR = 0.86, CI: 0.15–0.75, $p < 0.008$), and achieving CR, VGPR, or PR after induction chemotherapy (HR = 0.23, CI: 0.07–0.76, $p < 0.017$).

Similarly, higher albumin concentration (with every increase per 1 g/dl) (HR = 0.43, CI: 0.19–1.0, $p < 0.037$) and melphalan dose 140 mg/m² versus higher melphalan doses (HR = 0.48, $p = 0.081$) were associated with better OS. ECOG performance status of 2 versus 0 and 1 was the only pre-ASCT characteristic negatively affecting OS (OR = 3.5 95% CI: 1.51–8.28, $p = 0.004$). Shorter OS was associated with requirement for parenteral nutrition post ASCT (OR = 3.3, 95% CI: 1.44–7.72, $p = 0.005$), use of narcotic analgesics (OR = 2.7, 95% CI: 1.21–6.26, $p = 0.016$), grade 3 haemorrhagic complications (OR = 3.7, 95% CI: 1.07–13.1, $p = 0.039$), and cardiac complications (OR = 15.7, 95% CI: 3.07–80.8, $p = 0.001$).

The median follow-up time was 3.4 years. Detailed evaluation of prognostic factors affecting overall response rate (ORR), PFS, and OS after ASCT are shown in Table IV.

Discussion

Renal insufficiency in MM is known to carry poor prognosis [20], and achievement of normal renal function is not a realistic expectation for the majority of patients with DD CKD, in whom renal function did not improve after the first-line treatment [1, 3–6, 9]. Renal insufficiency is one of four myeloma-defining events (MDEs), in addition to anaemia, hypercalcaemia, and bone lesions, as the criteria for initiating MM systemic therapy [17, 21].

However, the treatment options for MM patients with renal failure have improved recently due to the availability of novel agents, which may be safely administered in moderate and end-stage renal insufficiency [22]. For patients with newly diagnosed MM and concomitant renal impairment,

proteasome inhibitors (e.g. bortezomib, carfilzomib, ixazomib) based induction is often associated with improvement in renal outcomes [22, 23].

Our group is not large but these are patients from the whole of Poland; the number of patients is also comparable to other studies regarding ASCT in MM patients with CKD [1, 4, 12]. In our series of 44 MM patients with advanced CKD, the frequencies of overall response \geq VGPR were similar before and after ASCT (40% vs. 45%, respectively). We can hypothesise that ASCT in the majority of cases consolidated the responses achieved before ASCT, and at least the responses did not worsen. Overall response to induction chemotherapy positively predicted response to ASCT. Attal *et al.* [24] reported that, in randomly selected MM patients for the treatment with and without ASCT, after four cycles of induction chemotherapy in both groups, an improved response was observed in the transplant setting [25]. However, there are no randomised trials comparing conventional chemotherapy to high-dose therapy and ASCT in MM patients with severe renal impairment, including DD MM patients, so we cannot estimate an absolute benefit of ASCT in DD MM patients regarding response, PFS, and OS. Augeul-Meunier *et al.* reported response to ASCT of at least VGPR in 58% of patients and in 96% of patients with bortezomib-based induction [12]. In contrast to the Augeul-Meunier *et al.* study, in which 56% of patients were treated with bortezomib-based induction, only 18% of our patients received frontline bortezomib. In Poland, bortezomib frontline treatment of patients with severe CKD has only been reimbursed by the National Health Fund since 2012 for transplant-ineligible and since 2015 for transplant-eligible patients (study duration 2004–2016).

It is controversial whether melphalan pharmacokinetics differ significantly in patients with and without renal insufficiency [26, 27], but if we assume that there is altered pharmacokinetics of melphalan, especially in MM patients with renal

Table IV. Univariate analysis of factors affecting ability to achieve complete response or very good partial response and overall survival after auto-SCT in patients with severe renal insufficiency

Characteristics	Predictors of CR + VGPR (logistic regression)			Predictors of PFS (proportional hazard regression)			Predictors of OS (proportional hazards regression)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age at diagnosis*	1.02	0.92–1.12	0.771	0.99	0.93–1.07	0.45	1.02	0.95–1.09	0.583
Age (diagnosis) ≥ 60 years vs. < 60 years**	1.36	0.33–5.61	0.673	1.4	0.58–3.39	0.45	1.29	0.53–3.12	0.567
Sex (woman vs. man)**	1.11	0.33–3.71	0.864	1.35	0.59–3.07	0.47	1.47	0.65–3.31	0.356
Diagnosis before 2012 vs. after 2012**	0.79	0.24–2.67	0.709	1.5	0.62–3.66	0.82	1.38	0.53–3.58	0.514
ECOG 2 vs. ECOG > 2**	0.46	0.1–2.07	0.309	1.57	0.61–3.97	0.35	0.28	0.12–0.66	0.0036
Albumin concentration*	0.79	0.3–2.08	0.627	0.41	0.18–0.93	0.03	0.43	0.19–1.0	0.037
β2-microglobuline concentration*	0.99	0.95–1.02	0.523	1	0.95–1.05	0.97	0.99	0.96–1.03	0.79
Calcium concentration*	2.91	0.33–25.6	0.336	0.76	0.20–2.72	0.67	0.55	0.13–2.25	0.405
Hb concentration*	1.00	0.72–1.38	0.982	0.92	0.67–1.27	0.62	1.043	0.74–1.48	0.813
Plasma cell count in bone marrow ≥ 60% vs. 60%**	0.99	0.97–1.01	0.434	1.02	0.99–1.04	0.07	1.01	0.99–1.03	0.170
Creatinine concentration at diagnosis*	0.86	0.72–1.04	0.13	0.98	0.85–1.12	0.71	1.02	0.91–1.2	0.720
Creatinine concentration at auto-SCT*	0.86	0.69–1.08	0.194	0.89	0.77–1.04	0.15	0.95	0.83–1.1	0.507
CD34(+) ≥ 4 ≥ 10 mln/kg body weight vs. < 4 × 10 mln/kg**	1.71	1.05–2.78	0.031	0.76	0.56–1.03	0.07	0.87	0.65–1.15	0.331
IgG concentration*	1.00	1.0–1.0	0.999	0.99	0.99–1.06	0.18	0.99	1.00–1.00	0.109
IgA concentration*	1.00	0.99–1.0	0.594	1.01	0.99–1.01	0.70	1.00	1.00–1.00	0.954
Time from diagnosis to auto-SCT*	1.00	1.0–1.0	0.406	0.99	0.99–1.00	0.07	1.00	1.00–1.01	0.341
Proteinuria vs. no proteinuria**	0.95	0.84–1.07	0.406	1.14	1.01–1.27	0.029	1.07	0.97–1.17	0.192
Light chains vs. no light chains**	1.00	1.00–1.00	0.513	1.00	1.00–1.00	0.57	1.00	1.00–1.00	0.979
FLC type lambda vs. other**	0.09	0.01–0.82	0.032	1.57	0.65–3.82	0.32	0.94	0.35–2.6	0.906
Lines of treatment before auto-SCT 1 line vs. ≥ 1 line**	1.75	0.47–6.50	0.403	0.38	0.13–1.11	0.08	0.42	0.14–1.2	0.115
MEL = 200 mg/m ² vs. other**	1.07	0.27–4.25	0.922	2.04	0.89–4.71	0.09	1.57	0.67–3.65	0.300
MEL = 140 mg/m ² vs. other**	1.03	0.3–3.58	0.965	0.86	0.15–0.75	0.008	0.48	0.22–1.09	0.081
Treatment with newer drugs in the first line vs. other**	0.73	0.22–2.44	0.607	1.16	0.52–2.59	0.71	0.69	0.31–1.56	0.380
Comorbidities 1 or > 1**	0.57	0.16–2.01	0.379	1.13	0.89–1.42	0.32	1.09	0.86–1.38	0.480
CR, VGPR or PR after chemotherapy vs. other response**	14.44	3.06–68.2	0.001	0.23	0.07–0.76	0.017	0.52	0.19–1.5	0.202
CR, VGPR after chemotherapy vs. other response**	11.57	1.31–103	0.028	0.67	0.27–1.63	0.38	0.89	0.35–2.3	0.810

Table IV. Cont.

Characteristics	Predictors of CR + VGPR (logistic regression)			Predictors of PFS (proportional hazard regression)			Predictors of OS (proportional hazards regression)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Post-transplant complications:									
Mucositis grade 3, 4 versus grade 1, 2 or no mucositis**	0.39	0.11–1.37	0.143	1.90	0.85–4.26	0.12	2.73	1.15–6.50	0.023
Parenteral nutrition**	0.32	0.08–1.23	0.097	2.48	1.10–5.60	0.023	3.33	1.44–7.72	0.005
Opioids use yes vs. no**	0.92	0.26–3.34	0.903	1.65	0.72–3.78	0.24	2.76	1.21–6.26	0.016
Diarrhea grade 3 vs. grade 1, 2 or no**	0.2	0.04–1.05	0.058	2.32	1.01–5.56	0.046	0.60	0.26–1.4	0.233
Infection of grade ≥ 3 vs. complications grade 1, 2 or no complications**	0.93	0.24–3.70	0.922	0.99	0.39–2.50	0.98	1.12	0.44–2.84	0.810
Haemorrhagic complication of grade 3 vs. no complications**		< 0.001 > 999.99	0.998	1.64	0.38–7.06	0.51	3.76	1.07–13.1	0.039
Neurological complication of grade 3 vs. grade 1, 2 or no complications**	0.61	0.05–7.3	0.697	0.67	0.09–5.04	0.70	2.13	0.48–9.4	0.317
Cardiac complication of grade 3 vs. grade 1, 2 or no complications**	***			14.9	2.46–90.2	0.003	32.0	5.22–196.8	0.0002
Neutrophil regeneration time*	1.04	0.86–1.25	0.72	1.00	0.90–1.13	0.88	0.47	0.93–1.16	0.472
Platelet regeneration time*	1.07	0.96–1.18	0.239	1.00	0.94–1.09	0.79	1.03	0.96–1.10	0.384
Platelet concentrate transfusion (number)*	1.08	0.94–1.24	0.294	0.98	0.872–1.096	0.70	1.03	0.95–1.12	0.460
Platelet concentrate (yes or no)**	2.24	0.38–13.1	0.372	1.57	0.53–4.72	0.42	2.35	0.70–7.94	0.170
Erythrocyte concentrate transfusion (number)*	1.05	0.92–1.19	0.507	1.01	0.90–1.13	0.88	1.06	0.96–1.17	0.239
Erythrocyte concentrate (yes or no)**	0.74	0.18–3.05	0.673	1.51	0.59–3.87	0.39	2.53	0.85–7.55	0.096
Hospitalisation duration*	1.00	0.96–1.04	0.832	1.01	0.98–1.04	0.37	1.02	0.97–1.07	0.097

failure, it may result in a higher concentration of the drug and higher incidence of clinical toxicity [27]. Melphalan is subject to spontaneous degradation [28, 29] and can be altered by a low concentration of albumin [27, 29]. In our study melphalan 140 mg/m² (MEL140), compared either to 100 mg/m² (MEL100) or to 200 mg/m² (MEL200), was associated with better PFS and OS. Mahindra *et al.* described 69 patients with severe RI (< 30 ml/min); 34 of 35 DD MM patients achieved dialysis independence post-ASCT [30]. Auner *et al.* showed an advantage of MEL200 in patients transplanted in less than partial response (HR = 0.5, MEL200 versus MEL140), and ASCT in VGPR or CR significantly favoured MEL140 for OS (HR = 2.02) [31]. Impaired renal function did not favour

the use of a lower melphalan dose with regards to non-relapse mortality or haematopoietic recovery. The dosing of melphalan in the treatment of MM seems to be crucial [4, 7, 11, 13, 31–35]. In the consensus statement of the International Myeloma Working Group regarding treatment of MM patients with renal impairment, high-dose melphalan 140 mg/m² is recommended rather than melphalan 200 mg/m² [24].

Patients with lambda light chain disease (10 out of 44) had a lower response rate than patients with other immunoglobulin isotypes. Lambda light chains are found to be more toxic to renal tubules and associated with shorter survival in comparison to patients with kappa light chain disease in other studies, as well [36, 37].

In patients with severe renal impairment, factors such as metabolic abnormalities, electrolyte, and fluid shifts may contribute to cardiac complications. Moreover, these patients may also have an increased risk of cardiovascular disease such as coronary heart disease, chronic heart failure, and other cardiovascular complications also without ASCT [38, 39].

With a median OS of 3.6 years and a median PFS of 2.3 years, our results are comparable to those observed in the other reports of MM patients with advanced CKD [4, 5], but they are inferior to those reported by Augeul-Meunier *et al.* [12], where OS and PFS were 6.3 years and 4.6 years, respectively. In our study the inclusion criteria also included the absence of renal response (any renal response) during the treatment period between diagnosis and ASCT according to IMWG criteria [13]. While in the study of Augeul-Meunier *et al.* of 26 patients who were DD on diagnosis 23 remained DD at ASCT, we did not include patients who became DID between induction chemotherapy and ASCT or who fulfilled criteria of minor response.

Three patients of our group (9%) became dialysis independent after ASCT. In the published studies the range of dialysis independence post ASCT varies between 3.4% and 24% [7, 10, 12, 37]. Lee *et al.* suggested that a higher rate of independence from dialysis after ASCT may be related to shorter duration of dialysis before ASCT (< 6 months) and recommend ASCT as consolidation to the first-line therapy [10]. Dialysis independence is a key to the improvement of the quality of life [40, 41]. Thus, it should be considered as an ultimate goal after ASCT in patients with advanced CKD. Unfortunately, the majority of DD MM patients at ASCT already have irreversible kidney damage, and there is infrequent recovery of renal function. Kidney transplantation could be considered in MM patients in complete remission with standard risk disease, good functional capacity, and minimal comorbidities, but the issue of relapse and disease recurrence remains a barrier in the situation of high demand for renal allografts [42, 43].

In our study, we observed that DID MM patients had shorter PFS than DD MM (statistical comparison was not possible), but overall survival was similar in DD and DID patients. Future studies may address the impact of earlier dialysis initiation in patients with MM with advanced CKD and their qualification to ASCT.

It was reported that of patients with eGFR lower than 40 ml/min at diagnosis, more than half had reversal of their renal injury (RI) upon institution of anti-myeloma induction therapy; however, about 40% of patients did not demonstrate any

reversal in renal function [44]. Furthermore, Gonsalves *et al.* demonstrated that even if a resolution of their RI upon receiving myeloma-directed therapy was achieved, the patients did not have equivalent survival outcomes to those of MM patients without RI. However, achievement of the reversal of RI was important for MM patients: patients who had RI at diagnosis but never recovered their renal function had a worse median OS when compared to patients who never had CKD (33 vs. 56 months, $p = 0.006$) [44].

Among patients with CKD at diagnosis, there remains a substantial proportion for whom achievement of renal response is not possible even with the use of novel drugs. Management of these patients requires a multidisciplinary team approach including tailored treatment decisions depending on renal function, timing of initiation of dialysis, age, performance status, comorbidities, and consideration for ASCT. Thus, future treatment strategies should include efforts to improve renal function before transplant and qualification of patients to ASCT [12, 31, 32]. The study has several limitations. We analysed retrospectively 44 multiple myeloma patients with severe renal impairment, who underwent ASCT in the years 2004–2016 on behalf of the Polish Myeloma Study Group. This cohort of patients was a heterogeneous group of patients with MM treated with different induction regimens and transplanted at various time points from the diagnosis of their disease both in DD and NRF patients; therefore, we concluded that there were no clear guidelines on how to treat such patients. Because only two centres in Poland perform auto-HSCT in patients with end-stage renal disease (ESRD) and multiple myeloma, we had a chance to collect all Polish data. Patients did not undergo kidney biopsy as other reasons for progressive renal injury (for example: advanced diabetes mellitus with complications, advanced polycystic kidney disease) were excluded, and the reason for ESRD was advanced stage of multiple myeloma (with CRAB symptoms not only R – renal). Cytogenetics and R-ISS might have helped to stratify risk in these patients, but these data were not available in a significant percentage of patients. The patients who were dialysis independent at diagnosis and became dialysis dependent due to disease progression were not included in the study because this group of patients have a different biology of multiple myeloma [45].

Prospective randomised studies in dialysis dependent patients may help to optimise the treatment of such patients to improve renal function and minimise treatment-related toxicity; however we are fully aware that enrollment for such a study might be a challenge as it was shown for the randomized controlled trials (RCTs) on the use

of high cut-off membrane for cast nephropathy in MM patients [46, 47].

In conclusion, optimal patient selection based upon good performance and higher albumin concentration (with every per increase of 1 g/dl), chemotherapy-responsive disease before ASCT, dose-adjusted melphalan, and aggressive post-ASCT supportive care are crucial to achieve acceptable results of treatment of MM patients with CKD, resulting in improved PFS and OS.

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Conflict of interest

The authors declare no conflict of interest.

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