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EDITORIAL

Allogeneic hematopoietic cell transplantation (allo-HCT) outcomes in myeloma patients on renal replacement therapy: a report from the Chronic Malignancy Working Party (CMWP) of the European Society of Blood and Marrow Transplantation (EBMT)

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Renal impairment is present in 20% of MM patients at diagnosis. Though rapid effective treatment may prevent progression to irreversible kidney injury, 1–5% of patients still ultimately require renal replacement therapy (RRT) [1, 2]. The median survival for myeloma patients with end-stage renal disease (ESRD) have been reported to be 18.3 months [3]. In addition to adverse FISH cytogenetic markers, renal impairment is therefore still a poor prognostic feature.

In 2018, 12,758 auto-HCT and 384 allo-HCTs were performed for the treatment of plasma cell disorders [4]. Although there is evidence of a graft-versus-myeloma effect, alloHCT in MM is associated with high transplant-related mortality (TRM) rates and is usually reserved for young patients with high-risk features [5]. Though the use of reduced intensity (RI) and non-myeloablative (NMA) conditioning chemotherapy is standard, the optimal approach for patients on RRT remains unclear [6, 7].

We are only aware of one report from the Fred Hutchinson Cancer Research Center presenting the outcomes of six patients on RRT who received RIC/NMA allo-HSCT between 1997 and 2014 [8]. Three of the six patients had MM and received tandem Auto-AlloHCT. Two were matched related donor transplants (one BM, one PB) who were conditioned with 2 Gy TBI followed by GvHD prophylaxis with Ciclosporin and Mycophenolate Mofetil (CSA/MMF). The first patient died of relapse at 10 months and the second of CMV pneumonitis at 11 months. The third patient received a haploidentical BM graft following Fludarabine (50% dose), post HCT Cyclophosphamide (day 3, 75% dose) and 2 Gy TBI. Immunosuppression consisted of MMF and Tacrolimus. This patient was alive 2 years post-transplant. The authors drew attention to the need for registries to report on such patients in order to address the feasibility and safety of allo-HSCT in ESRD patients requiring dialysis.

We sought information from EBMT centers on patients meeting the following eligibility criteria: diagnosis of MM, age >18 years at time of first allogeneic transplant and dialysis dependence at time of first allogeneic transplant. Four centers reported a total of six patients. As summarized in Table 1, the patients were transplanted between 2003 and 2016. The median age was higher (52 vs. 45 years) than those in the report by Sharma et al. All had presented with renal impairment at diagnosis. Three (50%) had high-risk FISH profiles (two 17p del, one *t*(14;16)). All six received an upfront auto-HCT after which three proceeded directly to an allo-HCT in a tandem approach; the other three had allo-HCT following relapses. All received peripheral blood stem cell products. Two received myeloablative conditioning and four received RI regimens. GvHD prophylaxis was standard (CSA/MMF) in addition to ATG or Campath. Although neutrophil engraftment was unremarkable, two patients failed to achieve platelet engraftment (>50,000/μL), this

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Table 1 Characteristics and outcomes of the six myeloma patients within the EBMT registry who were transplanted with stem cells from allogeneic donors while on hemodialysis.

Patient	#1	#2	#3	#4	#5	#6
Sex	Male	Female	Female	Male	Male	Female
Age at allo-HCT	58.40	39.87	36.05	57.55	52.03	52.65
Ig type	Light chain	IgG	Light chain	IgG	IgG	IgG
MM stage at diagnosis	IIIB	IIIB	IIIB	IIB	IIIA	IIIB
Cytogenetics abnormality	Not done	trisomy 9	del(13), *t*(14;16)	del(17)(p13)	Normal	del(17)(p13)
Dialysis dependent at diagnosis	Yes	Yes	Yes	Yes	Yes	No
Dialysis dependent at allo	Yes	Yes	Yes	Yes	Yes	Yes
Interval auto to allo (months)	6.39	3.13	4.25	35.23	3.89	7.08
Donor type	Identical sibling	Identical sibling	Matched unrelated	Matched unrelated	Identical sibling	Matched unrelated
Conditioning regimen	RIC: Flu + Mel	RIC: Flu + Mel	RIC: Flu + Mel + ATG	MAC: Bu + Cy + ATG + TBI (9Gy)	RIC: Flu + Mel + Campath	MAC: Bu + Thiotepa
Prophylaxis regimen	CsA + MMF	CsA + MMF	CsA + MMF	CsA + MMF	CsA alone	Cy + CsA
Disease status at allo-HCT	CR	VGPR	PR1	Progression	Stable disease	PR1
Best response of allo-HCT	CR	VGPR	CR	PR	PR	PR
Platelets $\geq 20 \times 10^{-9}$/L reached	No	Yes	Yes	Yes	Yes	Yes
Interval platelets $\geq 20 \times 10^{-9}$/L reached (in days)	NA	17	29	26	18	36
aGVHD	No	No	No	No	No	Yes
cGVHD	No	No	Extensive	No	No	No
Transfusion independent post allo	No	Yes	Yes	No	No	Yes
Erythropoietin use post allo	No	Yes	No	No	No	Yes
Anti-myeloma drug post allo	No	No	No	No	Yes	No
Relapse status	No	No	No	No	Relapse	No
Interval from allo to first relapse (in months)	NA	NA	NA	NA	31.51	NA
Survival (in months)	4.04	3.02	170.91	3.81	126.52	4.70
Main cause of death	Infection	TRM: decompensated right heart failure	Alive	Infection	Relapse/ progression	Infection

M male, *F* female, *IS* identical sibling, *MUD* matched unrelated donor, *Ig* immunoglobulin, *ISS* International Staging System, *CsA* ciclosporin A, *MMF* mycophenolate mofetil, *CR* complete remission, *PR* partial remission, *VGPR* very good partial remission, *TRM* transplant related mortality, *PFS* progression free survival.

was not associated with conditioning regimen intensity. Five of the six patients had suboptimal responses pre-alloHCT and three upgraded their responses to ≥PR. Three of the patients became transfusion-independent with two continuing to require erythropoietin. Four patients died within 6 months and one patient at 126 months. Infections were the most common cause of death. Four patients in remission post-allo died due to infections or HCT related complications. Relapse was only observed in one patient who received four further lines of anti-myeloma treatment post-transplant and subsequently died of disease progression at 126 months. This patient's response pre and post allo were stable disease and PR, respectively. The longest survivor is still alive at 170+ months while on RRT without relapse but extensive cGvHD. This patient, the youngest in our cohort, had high-risk cytogenetics with *t*(14;16) and 13q del at diagnosis. These results provide evidence of the anti-myeloma activity of allo-HCT even in patients on RRT. However, the infectious morbidity was significant.

A strategy to mitigate TRM by reducing the doses of drugs in the conditioning regimen was of no clear benefit and resulted in a shortening of PFS [8]. Conversely, our two patients with myeloablative conditioning died of infections <5 months post alloHCT. Nonetheless, two of our six patients survived for 126 and 170 months, respectively, following RIC, evidence that there may be a role for alloHCT in selected young, high-risk patients with ESRD. Even in the current era of potent new proteasome inhibitors and monoclonal antibodies, renal impairment in MM patients remains a challenge.

In the setting of a related donor allo-HCT, renal transplantation is an option. There are case reports and series of sequential auto-HCT and kidney transplants [9, 10]. Early relapse of myeloma following kidney transplantation, and infectious morbidities are the main obstacles to this approach [11]. Furthermore, loss of kidney graft function has been observed following relapse of myeloma. Patients lacking high-risk features or evidence of residual myeloma prior to kidney transplantation are the best candidates for such living donor renal allografts. There are reports of successful combined allo-HCT and living donor kidney transplants including a recent series of six patients diagnosed with hematological malignancies, five of whom were conditioned with fludarabine, cyclophosphamide, and total-body irradiation, who underwent combined HCT/kidney transplantation from haploidentical donors [12]. One patient experienced a myeloma relapse at 30 months after allo-HCT and died at 4 years. Overall, four of six patients remain alive, without disease relapse and with long-term renal rejection-free survival. Such combined approaches carry the potential for allo-immune tolerance and avoid the need for continuous immunosuppression and the associated toxicities. In our case series, there were no such combined allo-HCT and kidney transplants. However, this data may provide further guidance to clinicians considering allo-HCT in this rare patient population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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