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Letter to the Editor

J Hematol. 2025;14(1):38-42

Allogeneic Stem Cell Transplantation for High/Ultra High-Risk Multiple Myeloma

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To the Editor

The outlook of multiple myeloma (MM) has significantly improved over the past 20 years after the discovery of immunomodulatory drugs. Autologous transplantation has been the standard treatment in transplant-eligible patients for the past few years [1]. However, none of these therapies are curative. Newer approaches to improve outcomes are necessary. Unlike other newly developed treatments for MM, allogeneic transplants (AlloT) can cause a graft-versus-myeloma effect, enabling long-term survival or even a cure for some patients [2].

However, AlloT has become less attractive due to its high mortality rate from graft-versus-host disease (GVHD) and other complications [2]. With the recent development of reduced-intensity conditioning (RIC), early mortality can be reduced and AlloT can be applicable to older patients and those with comorbidities, improving outcomes in people living with the disease [3]. In particular, there may be a place for AlloT in younger patients with greater risk features, because these patients have few other curative options due to the known short progression-free survival (PFS) in high-risk myeloma [4].

Considering the limited data available and to better understand the outcomes for patients with MM treated with AlloT, we conducted a retrospective analysis at our mid-sized transplant center to evaluate AlloT for MM and summarized the information in Table 1. From 2003 to 2010, eight patients received AlloT, comprising six males and two females. The median age at diagnosis was 51 years (35.7 - 72.4), and the median age at transplant was 52.5 years (36.4 - 72.8). Four patients were Caucasian, three were African American, and one was Asian. Five patients were classified as R-ISS stage II refractory/relapsed MM, and three patients were classified as stage IIIA refractory/relapsed MM. Six patients had undergone previous autologous transplant and showed continued disease progression prior to their AlloT. Seven patients received AlloT from human leukocyte antigen (HLA)-matched sibling, and one patient received a syngeneic transplant from an identical twin. The syngeneic transplant was included because, although it has a similar immunological profile to autologous transplantation, syngeneic transplants are unique, like AlloT, in that the infused hematopoietic stem cells are free from damage caused by cytotoxic chemotherapy and from the risk of leukemic contamination.

Additionally, the initial therapies and conditioning differed slightly. Therapies were reported as their common acronyms for the sake of verbosity and explained in the acronyms section. A swimming plot showing the outcomes and treatment of each patient is included in Figure 1. One patient received VAD, DT-PACE, VTD-PACE, and VelDex, while four patients received LenDex. For conditioning, three patients had BuCy, four had FluCy, and one had HDM. No patients had high-risk cytogenetics. The median time from diagnosis to AlloT was 0.92 years. The median overall survival (OS) was 6.7 years (range: 1.8 - 20.1 years), with 75% and 62.5% alive at 1 and 5 years, respectively. For the four RIC patients, OS was 50% at 2 years and 50% at 5 years, while for those receiving myeloablative therapy, OS was 100% at 2 years and 75% at 5 years.

Two patients had mild acute GVHD, while five patients experienced chronic grade I GVHD of the skin, liver, and bowel, which all improved and were stable with immunosuppressive therapy (including varying combinations of prednisone, tacrolimus, sirolimus, triamcinolone, rituximab, mycophenolate mofetil, and cyclosporine). One patient showed no signs of GVHD but had a sudden venous thromboembolism, leading to a pulmonary embolism and death.

Following transplant, seven patients entered partial remission. Five of those patients relapsed, and one patient died shortly after transplant. Of the two non-relapse patients, one died due to complications of immunosuppressive therapy, and one had minimal residual disease (MRD) but transferred care. Of the five patients who relapsed, the median time to relapse was 3.64 years (0.21 - 9.33). One patient did not receive further treatment. Another patient received MPR (four cycles), KD (six cycles), and pomalidomide (one cycle) after transplant following locally recurrent disease and achieved complete remission with MRD-negative disease. One patient received CyBorD-R (11 cycles), then GMCSF, and eventually thalidomide

Manuscript submitted October 27, 2024, accepted December 4, 2024
Published online December 31, 2024

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doi: https://doi.org/10.14740/jh1380

Table 1. Reported Outcomes and Demographics of Single-Center AlloT

Demographics	
Gender	Male (n = 6, 75%), female (n = 2, 25%)
Race	Caucasian (n = 4, 50%), African American (n = 3, 37.5%), Asian (n = 1, 12.5%)
Median age at diagnosis	51 years (35.7 - 72.4)
Median age at transplant	52.5 years (36.4 - 72.8)
Disease characteristics	
R-ISS stage at diagnosis	Stage II (n = 5, 62.5%), stage IIIA (n = 3, 37.5%)
Previous autologous transplant	n = 6, 75%
Transplant characteristics	
Transplant type	HLA-matched sibling (n = 7, 87.5%), syngeneic twin (n = 1, 12.5%)
Median time to AlloT from diagnosis	0.92 years
Initial therapies	VAD (n = 1, 12.5%), DT-PACE (n = 1, 12.5%), VTD-PACE (n = 1, 12.5%), VelDex (n = 1, 12.5%), LenDex (n = 4, 50%)
Conditioning regimens	BuCy (n = 3, 37.5%), FluCy (n = 4, 50%), HDM (n = 1, 12.5%)
GVHD incidence	Mild acute (n = 2, 25%), chronic grade I (n = 5, 62.5%), none (n = 1, 12.5%)
Survival outcomes	
Alive at 1 year	75%
Alive at 5 years	62.50%
RIC OS	50% (2 years), 50% (5 years)
Myeloablative OS	100% (2 years), 75% (5 years)
Median overall survival	6.7 years (1.8 - 20.1)
Relapse and mortality	
Relapse rate	71% (10 year)
Median time to relapse	3.64 years (0.21 - 9.33)
Time to death post-transplant	7.89 years (0.37 - 17.6)

AlloT: allogeneic transplantation; GVHD: graft-versus-host disease; RIC: reduced-intensity conditioning; OS: overall survival; VAD: vincristine, doxorubicin, and dexamethasone; DT-PACE: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VTD-PACE: bortezomib dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VelDex: bortezomib and dexamethasone; LenDex: lenalidomide and dexamethasone; BuCy: busulfan and cyclophosphamide; FluCy: fludarabine and cyclophosphamide; HDM: high-dose melphalan; HLA: human leukocyte antigen.

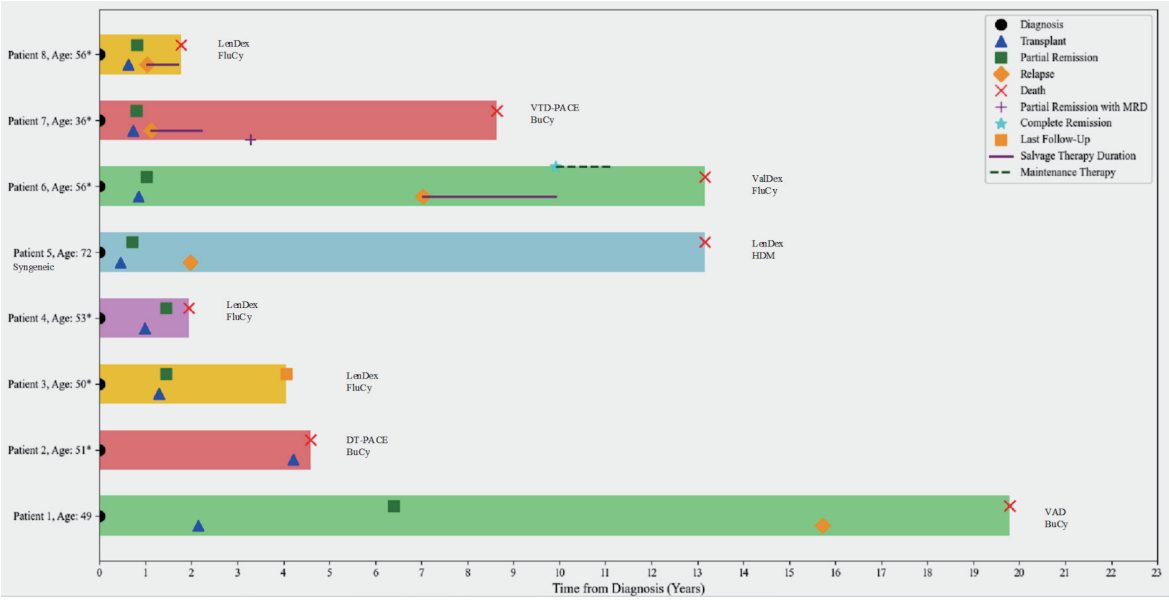

Figure 1. Swimming plot of allogeneic transplant outcomes for each patient. VAD: vincristine, doxorubicin, and dexamethasone; DT-PACE: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VTD-PACE: bortezomib dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VelDex: bortezomib and dexamethasone; LenDex: lenalidomide and dexamethasone; BuCy: busulfan and cyclophosphamide; FluCy: fludarabine and cyclophosphamide; HDM: high-dose melphalan; MRD: minimal residual disease.

followed by maintenance lenalidomide, ultimately achieving partial remission with MRD. Another patient received lenalidomide, then began salvage treatment with DaraDex and then lenalidomide as maintenance and eventually achieved complete remission. The fourth patient had persistently progressive disease treated with CyborD, then Velcade, then CTD (two cycles), and finally PAN-VelDex and eventually entered palliative care. Ultimately, seven of the eight patients have died, and one has been lost to follow-up due to transfer. The median time to death following transplant was 7.89 years (0.37 - 17.6).

Recently, Afrough et al completed a retrospective analysis of 33 AlloT in patients with newly diagnosed high-risk MM from 1994 to 2016 [5]. A median OS of 131.9 months and a 5-year OS of 58% were reported in this series. The authors also showed that AlloT procedures performed between 2013 and 2016 might have better median PFS and OS than those performed between 1994 and 2004 [5]. Additionally, Table 2 includes recent study results [3, 6-10] to summarize the AlloT outcomes.

The outcomes observed in our study align with and differ from prior reports on AlloT in MM in several aspects. Notably, the median OS in our cohort was 6.7 years, with a 5-year survival rate of 62.5%, which is comparable to the findings by Afrough et al [5], who reported a median OS of approximately 11 years and a 5-year OS of 58% in a larger cohort of 33 patients treated between 1994 and 2016. However, other studies, such as those by Hayden et al [2], reported 2-year OS rates as low as 25% in certain subgroups, particularly those receiving myeloablative conditioning regimens, emphasizing the impact of transplant intensity on outcomes. Furthermore,

Table 2. Summary of Recent Allogenic Transplant Outcome Data

References	N	Overall survival		Progression-free survival		Relapse rate		
		2-year	5-year	2-year	5-year	2-year	3-year	5-year
Hayden et al 2021 [9]	215	38%[d]	25%[d]	17%[d]	6%[d]	68%[d]	-	79%[d]
Sahebi et al, 2019 [7]	96	48%	-	17%	-	56%	-	-
Hayden et al, 2020 [3]	344	-	39%[a], 45%[b], 19%[c], 34%[d]	-	15%[a], 17%[b], 14%[c], 15%[d]	-	52.7%[a], 50.2%[b], 48.1%[c], 58.3%[d]	-
Schmidt et al, 2023 [10]	91	-	20%[a], 8%[b], 28%[c]	-	14%[a], 0%[b], 20%[c]	-	-	-
Jurgensen-Rauch et al, 2021 [8]	37	-	66%[a]	-	48%[a]	-	-	50%[a]
Eisfeld et al, 2020 [6]	90	53%	39%	36%	25%	-	-	-

All values are reported as percentages of the cohort that died, progressed, or relapsed over the defined time-period. [a]Reduced intensity conditioning, [b]non-myeloablative, [c]myeloablative conditioning, and [d]conventional autologous hematopoietic cell transplantation are used to achieve a minimal disease burden prior to allografting.

the relapse rate in our study was 71% at 10 years, which aligns with relapse rates ranging from 50% to 79% reported in larger series, such as those from the European Society for Blood and Marrow Transplantation [3, 6, 7]. These findings highlight the challenges of disease progression post-AlloT, even with favorable initial responses.

There are many new, promising treatments in the treatment of MM, such as chimeric antigen receptor (CAR) T-cell therapy and bispecific antibodies. Li et al found that the median OS for patients receiving CAR T-cell therapy was 42.8 months, but these patients may also experience intractable complications such as cytokine release syndrome and neurotoxicity [11]. Also, CAR-T products have long manufacturing processes, so patients with relapsed or refractory MM that are enrolled for CAR-T therapy may not even receive it due to disease progression. Bispecific antibodies, on the other hand, had a median progression-free period of 11 months, and cytokine response syndrome occurred in 72% of the patients [12].

Another new aspect of MM care is MRD negativity. MRD status was not previously available for consideration at the time of AlloT in our patients or in the reported literature. MRD negativity is an important prognostic factor as it is shown to have prolonged overall and PFS periods, as well as reduced risk of death from disease progression irrespective of their molecular status and disease stage [13]. MM is considered high risk when it has a predicted OS of less than 3 years. Patients with ultra-high-risk MM have a predicted OS of less than 2 years, typically characterized by features such as certain cytogenetic/genetic abnormalities or having relapsed within 1 year of AutoT. However, the prognosis of high-risk patients achieving sustained MRD negativity is close to that of patients with standard-risk MM [13].

In the current era of CAR T-cell therapies and bispecific antibodies, the role of allogeneic hematopoietic stem cell transplantation (HSCT) in MM has become highly restricted, potentially limited to consolidation in cases of refractory or ultra-high-risk disease, where other therapies have failed to achieve MRD negativity. Other consolidation strategies for high-risk MM include the use of double autologous stem cell transplantation, intensified regimens combining proteasome inhibitors and immunomodulatory drugs, bispecific antibodies and CAR-T therapy. However, none of these options are potentially curative, and these patients will eventually relapse. Future research should explore biomarkers or genetic profiles that can help identify patients who may still benefit from consolidation.

Acknowledgments

We thank the staff of the Georgia Cancer Center and Wellstar MCG Hospital for their efforts in care and research.

Financial Disclosure

JC discloses relationships with Novartis, Pfizer, Sun Pharma, Syndax, Nerviano, Lilly as a consultant. He reports receiving research funding from Novartis, Sun Pharma, Ascentage, and AbbVie. He is also a current holder of stock options and has membership on the Board of Directors at Biopath Holdings. VK has relationships with Pfizer and Novartis. All other authors have no financial disclosure to report.

Conflict of Interest

The authors declare that they have no conflict of interest concerning this article.

Informed Consent

Not applicable.

Author Contributions

CW, VK and JC designed the research. CW and RV collected and analyzed data. CW, RV, AS, MG, AJ, and VK wrote and approved the final paper.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

MM: multiple myeloma; AlloT: allogeneic transplantation; AutoT: autologous transplantation; GVHD: graft-versus-host disease; RIC: reduced-intensity conditioning; OS: overall survival; PFS: progression-free survival; MRD: minimal residual disease; VAD: vincristine, doxorubicin, and dexamethasone; DT-PACE: dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VTD-PACE: bortezomib dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; VelDex: bortezomib and dexamethasone; LenDex: lenalidomide and dexamethasone; BuCy: busulfan and cyclophosphamide; FluCy: fludarabine and cyclophosphamide; HDM: high-dose melphalan; MPR: melphalan, prednisone, and lenalidomide; KD: carfilzomib and dexamethasone; CyBorD-R: cyclophosphamide, bortezomib, dexamethasone, and rituximab; GMCSF: granulocyte-macrophage colony-stimulating factor; CTD: cyclophosphamide, thalidomide, and dexamethasone; PAN-VelDex: panobinostat, bortezomib, and dexamethasone; DaraDex: daratumumab and dexamethasone; CAR: chimeric antigen receptor

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