Autologous/Allogeneic Hematopoietic Cell Transplantation (HCT) Versus Tandem Autologous Transplantation for Multiple Myeloma - Comparison of Long Term Post Relapse Survival

Published version:

DOI:10.1016/j.bbmt.2017.10.024

(Article begins on next page)

BIOLOGY OF BLOOD AND MARROW TRANSPLANTATION. None, 2017, pp: 1-8

DOI: 10.1016/j.bbmt.2017.10.024

Autologous/allogeneic hematopoietic cell transplantation (HCT) versus tandem autologous transplantation for multiple myeloma – Comparison of long term post relapse survival

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Word Count: Abstract: 270, Manuscript: Body Text : 2,541

Tables: , Figures:

Running title: Post-relapse OS in autologous versus allogeneic transplant in myeloma

Keywords: allogeneic transplant, myeloma, relapse, survival

Abstract

We compared post-relapse overall survival (OS) after autologous-allogenenic (auto/allo) versus tandem autologous (auto/auto) hematopoietic cell transplantation (HCT) in multiple myeloma (MM). Post-relapse survival of patients receiving an auto/auto or auto/allo HCT for MM and prospectively reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) between 2000 and 2010 were analyzed. 404 patients (72.4%) relapsed in the auto/auto group and 178 patients (67.4%) relapsed in the auto/allo group after a median follow up of 8.5 years. Among auto/allo patients, 46% of relapses occurred in < 6 months from 2nd HCT, compared to 26% in the auto/auto group. The 6 year post-relapse survival of the auto/allo group (44%) was superior compared to auto/auto group (35%) (p=0.05). 101 patients in auto/allo patients died due to MM (69%) vs. 229 (83%) deaths in auto/auto group. In multivariate analysis, both cohorts had a similar risk of death in the 1st year after relapse (hazard ratio (HR) of 0.72; p=0.12). However, for time points beyond 12 months after relapse, patients in the auto/allo group had superior OS compared with auto/auto cohort (HR for death in auto/auto =1.55; p=0.005). Other factors associated with superior survival were enrollment in a clinical trial for HCT, male sex and novel agent use at induction before HCT. Survival after relapse is superior in auto/allo HCT recipients compared to auto/auto HCT recipients. This likely reflects an improved response to salvage therapy, such as immunomodulatory drugs, potentiated by donor-derived immunologic milieu. Further augmentation of post-allotransplant immune system with new immunotherapies such as monoclonal antibodies, check point inhibitors and others should be studied.

Introduction

The survival of patients with multiple myeloma (MM) has improved significantly over the past two decades.[1] High-dose chemotherapy with autologous hematopoietic cell transplantation (HCT) improves survival compared with conventional chemotherapy or novel agents.[2,3] However, despite high remission and survival rates, the risk of progressive disease remains a concern after both single and tandem HCT.[4]

Allogeneic HCT, which provides a tumor-free graft, has been considered as an alternative treatment with curative potential for patients with myeloma. The potential long term benefit is attributed to the graft-versus-myeloma (GVM) effect, best demonstrated by higher molecular remissions after donor lymphocyte infusions.[5] Early studies evaluating allogeneic HCT with myeloablative conditioning regimens demonstrated improved molecular remissions and lower rates of relapse, but were hindered by high treatment-related mortality.[6] More recently, the combination of autologous transplant followed by reduced intensity allogeneic transplant appears to retain the potent GVM effect while reducing treatment-related mortality (TRM).[7]

To date, five large prospective trials[8-13] involving approximately 1600 patients have shown a lack of overall survival (OS) advantage with the auto/allo HCT approach, while two trials[14-16] involving approximately 500 patients have demonstrated a survival benefit. Differences in outcome can be attributed to differences in study design, including the target population, conditioning regimen, sibling donor availability, and length of follow up (Supplemental Table 1). Two published meta-analysis also did not show an OS benefit for auto/allo over auto/auto HCT.[17,18]

In the largest trial by Krishnan et al,[12] outcomes of 710 MM patients receiving auto/allo HCT (226 patients, low dose total body irradiation conditioning for allo HCT) vs. tandem auto HCT (484 patients) by biological assignment (based on availability of human leukocyte antigen (HLA)-matched sibling donor) were compared. There was no significant difference in 3-year progression free survival (PFS)/OS between auto/allo HCT and tandem auto-HCT group (PFS: 43% vs. 46%, p= 0.671 and OS: 77% vs. 80%, p=0.191). A criticism of the study was the follow up time of 36 months, which was thought to be too short to reveal the possible favorable effects of an allo HCT. One of the unanswered questions of this trial as well as other auto/allo HCT trials is not only comparisons of PFS with tandem auto-HCT vs auto/allo HCT with longer follow-up, but also the long term impact of these treatment modalities. Since these trials used transplant in the upfront setting, patients had many treatment choices at the time of relapse.

Most of the trials above measured OS from the time of transplant and there have been reports of OS for MM in CIBMTR population after alloHCT [20, 29]. Gahrton, et al. have demonstrated that survival after relapse was superior in the auto/allo recipients compared with auto/auto HCT.[16] We therefore conducted a retrospective analysis to study the outcome of patients who relapse after auto/allo HCT versus auto/auto HCT.

Patients and Methods

Patients

There were 1679 patients who either received an upfront auto/auto (n=1186) or auto/allo HCT (n=569) for MM reported to the CIBMTR between 2000 and 2010 in North America. We excluded patients who had relapsed between the 2 transplants. Patients who received their 2nd transplant later than 6 months after 1st transplant were also excluded. After exclusion, there were 558 patients in auto/auto group and 264 patients in auto/allo group remained for further analysis. We studied patients who either relapsed or progressed and the term "relapse" in this analysis will represent both relapsed and progressive disease categories. Detailed eligibility criteria are shown in Figure 1 and Supplemental table 2. For allo HCT, we selected only peripheral blood stem cell source. High risk myeloma was defined as del17p, t(4;14), t(14;16), hypodiploidy (<45 chromosomes excluding -Y) or chromosome 1 p and 1q abnormalities.[19]

Statistical analysis

We compared post-relapse OS between auto/allo HCT cohort versus the auto/auto HCT cohort. Our secondary objective was to identify factors associated with long term survival after tandem transplantation (auto/allo or auto/auto).

We tested differences between the patient groups using the chi-square test and Kruskal-Wallis test for categorical and continuous variables, respectively. For univariate analyses, survival probabilities were calculated by using the Kaplan-Meier estimator with the variance estimated by Greenwood's formula.

Post-relapse survival was defined as the interval between first progression or relapse after completion of HCT and death with survivors censored at last follow up. Multivariate analysis of post-relapse OS was conducted using the Cox proportional hazards regression model. The transplant group, auto/auto versus auto/allo, was considered as the main effect. Other factors tested included age at 1st transplant, gender, Karnofsky performance status (KPS) at 2nd transplant, clinical trial enrollment, advanced stage at diagnosis (International Staging System III or Durie Salmon Stage III), lines of pre-transplant chemotherapy, pre-transplant novel (thalidomide, lenalidomide, bortezomib, pomalidomide and carfilzomib) therapy use, time from diagnosis to 1st transplant, disease status prior to 2nd transplant and time from 2nd transplant to relapse. All statistical tests were two-sided with a significance level of 5%.

Results

404 patients (72.4%) relapsed in the auto/auto group and 178 patients (67.4%) relapsed in the auto/allo group. The baseline characteristics of relapsed patients are shown in table 1.

Patient Characteristics

The majority of patients were male (58 % auto/allo and 60% in auto/auto group). The median age was lower in auto/allo patients at 51 years and 56 years in auto/auto group. The majority of patients had a KPS of ≥90% (71% and 60% for auto/allo and auto/auto, respectively). Five percent of patients in both groups were high-risk by cytogenetics, though data were missing in 35% of patients.

Transplant-related characteristics

1st transplant-related characteristics

73% of auto/allo patients and 90% of auto/auto patients received 1-2 lines of therapy before their 1st transplant indicating that the cohorts in this study were less heavily pretreated. The use of novel agents at induction was higher in auto/auto group (73%) versus the auto/allo group (58%) (p=<0.001). The incidence of partial response or higher (≥PR) before 1st HCT was also higher in auto/auto group (88%) than auto/allo group (82%) ($p < 0.001$). The majority of patients received melphalan at 200 mg/m^2 at first transplant in both groups. The median time from diagnosis to 1st HCT was 8 months in auto/allo group and 7 months in auto/auto patients again reflecting the upfront use of HCT in these cohorts.

2nd transplant-related characteristics

The complete response (CR) rate before the 2nd HCT was 19% and 14% in auto/allo and auto/auto group, respectively. The 2nd HCT was done within 3 months of the 1st HCT in 39% of patients in auto/allo group and 29% in auto/auto group.

In the auto/allo group, the majority of the patients (96%) received HLA-matched donor grafts and matched unrelated donors represented only 4% of the group. Almost all patients who received auto/allo HCT were conditioned with myeloabalative regimen (table 1). Cyclosporine and mycophenolate mofetil were the most commonly used drugs for graft vs. host disease (GVHD) prophylaxis in 65% of the auto/allo group.

There were 18 patients who received donor lymphocyte infusion (DLI) and only one patient received DLI as a planned therapy and remaining 17 patients received DLI for relapse after allogeneic transplant. The patients who received DLI didn't have superior OS compared to patients who didn't receive DLI (Supplemental table 3).

Post 2nd transplant outcomes

28.7 % of patients in the auto/auto group received some form of maintenance chemotherapy as opposed to 8.8 % in auto/allo group ($p<0.001$). In the auto/allo cohort, the incidence of grade II-IV acute GVHD (aGVHD) was 24 % and grade III-IV was 11%. 58% of patients developed chronic GVHD (cGVHD). The median follow up time from relapse was 102 months for auto/allo and 99 months for auto/auto group, respectively. High proportion of patients (46%) relapsed within 6 months after auto/allo HCT but only 26% of auto/auto patients relapsed in the same time frame. There were more relapse in auto/auto group (39%) than auto/allo patients (24%) 2 years after 2nd HCT.

<u>Post-relapse OS</u>

In univariate analysis, the 6 year probability of survival in auto/allo group was 44% compared to 35% in auto/auto group ($p=0.05$). (Table 2).

After a median follow up of 102 months, 101 patients in the auto/allo group had died, 70 patients (69 %) were due to myeloma and 4 patients (4%) from GVHD (Table 3). 16 patients (16%) died due to infections in auto/allo patients compared to 8 patients (3%) in auto/auto patients. In the auto/auto group, 229 patients died after median follow up of 99 months, 189 patients (83%) were due to MM. TRM was 6% in auto/allo group and 1% in auto/auto group at 1 year (Supplemental table 4).

The median survival from diagnosis to death for auto/allo patients group was 86.3 months (11.4-183.8) vs. 75 months (10.9-173.3) in auto/auto group. Similarly OS probability at 7 years from diagnosis were 55.7 % in auto/allo group and it was 51.3% ($p=0.33$) in tandem auto group.

On multivariate analysis, a pattern of differential time-dependent risk of mortality was observed. Both cohorts had a similar risk of death in the 1st year after relapse (HR of 0.72; p=0.12). However, beyond 12 months post-relapse, patients in the auto/allo group had a superior OS compared with auto/auto cohort (HR for death in auto-auto=1.55; p=0.005) (Table-4).Significant co-variates associated with superior post-relapse survival included enrollment in a clinical trial for HCT (HR for death in patients not on trial= 1.39; p=0.005), male sex (HR for death in female patients= 1.27; p=0.03) and the use of novel agent/s in pre-transplant chemotherapy (HR of death for non-novel agent therapy=1.43; p=0.0023) (Table 4).

When OS was adjusted using statistically significant variables from multivariate analysis (i.e. differential time effect of 12 months, sex, clinical trial enrollment and novel agent use), the probability of OS was higher for auto/allo patients (45%) than auto/auto patients (35%) at 6-year after relapse (p=0.035) (Supplemental table 5). Figure 2 represents graphic presentation of adjusted post-relapse survival.

Discussion

In this large retrospective registry study analyzing long term post-relapse survival among MM patients who underwent auto/auto versus auto/allo HCT, we found that patients who underwent auto/allo HCT had a long term post relapse survival advantage beginning after 12 months post-relapse. Similar findings which were initially reported by Gahrton et al.[16] in allogeneic HCT with matched sibling donors are confirmed in our data using a larger real world population of related and unrelated grafts.

Clinical trial enrollment was also found to have positive effect on OS, possibly due to better patient selection and closer monitoring. Novel agent therapy at induction also decreased risk of death compared to standard chemo therapy. In multivariate analysis of OS, male sex was found to have reduced risk of death but age was not found to have significant impact on survival. The median age for auot/allo group is younger (51 vs. 56) compared to auto/auto group. It is probably due to selection bias to choose younger patients by the treating physicians to proceed with auto/allo HCT. The median age for auto/allo group is also younger compared to auto/auto group in largest randomized auto vs. allo HCT trial reported by Krishnan et al.[12]

CR rate after first HCT were lower in our study compared to auto vs. allo HCT trial reported by Krishnan et al[12] which may indicate a bias toward doing a 2nd HCT among patients with suboptimal CR rates to 1st HCT.Benefit for allogeneic HCT generally takes time to be observed, as seen in the European Blood and Marrow Transplant study[15,16] which showed no significant difference in the groups at three years but follow up at five and eight years demonstrated the advantage of allogeneic HCT. Our analysis, with a median follow up time of 102 months (8.5 years) after relapse confirms a statistically significant adjusted survival benefit for the allogeneic cohort versus tandem autologous HCT (p=0.035) (Supplemental Table5).

Almost half the relapses (46%) in the auto/allo group happened early i.e. within six months after the second HCT, versus one quarter of the relapses (26%) in the auto/auto group. This was in spite of the fact that 90% of patients in both group achieved ≥PR or better before 2nd HCT. The difference is likely secondary to the reduced intensity conditioning (RIC) for allo HCT which relies on donor lymphocyte effect (that may take up to a year to fully develop) to prevent relapses vs. myeloablative conditioning (73% of patients received 200mg/m2 of melphalan) in the auto/auto group. Selection bias by treating physicians to enroll MM patients with more aggressive/higher risk disease could have been a factor contributing to higher relapses in auto/allo patients. Similar early relapses post-allogeneic HSCT were also noted in other studies.[12,20,21] In addition, a higher usage of post-transplant maintenance therapy in the auto/auto patients (28.7% vs. 8.8%) could have played a role in delaying early relapse post auto transplant vs. post allo transplant. Lower usage of maintenance therapy especially after auto HCT reflects the era of our study (2000-2010) when the maintenance therapy was not commonly used.

The Incidence of cGVHD seems to be higher in our trial (58%) compared to findings from others[20,22] but we were unable to evaluate the effect of cGVHD on post relapse survival as cGVHD is a time-dependent covariate starting at the time of transplant and our study starts from time of relapse. We do note that 24% of our patients had history of grade II-IV aGVHD; presumably, aGVHD predated the relapse after allogeneic HCT as the median time to relapse was 9 months.

Our study focused on patients who received their allogeneic HCT as a tandem approach after a prior auto HCT within six months after first transplant. We excluded patients undergoing allo HCT for relapse after an auto HCT. The median interval between diagnosis and first HCT was seven months in the auto/allo group. The overwhelming majority of allo HCT donors in our study were HLA-matched siblings (96%). The study population of auto/allo HCT matches a better risk group identified by CIBMTR review of 1207 patients who underwent allogeneic HCT from 1989 to 2005 which showed that both factors (>24 months interval between diagnosis to allogeneic HCT and unrelated donor graft) are poor prognostic indicators for survival.[20]

A major limitation of our study was our inability to measure the significance of high-risk cytogenetics which contributed only 5% of study population while approximately 35% of cytogenetic data were missing. This is representative of the time period in our study and the evolution of what constitutes high-risk cytogenetics in MM over time. Additionally, we do not have other potentially relevant factors such as details on salvage therapy and response to salvage therapy after relapse following 2nd HCT as they were not regularly reported to the database. The important strength of our study is that it included a large number of patients and multiple transplant centers reflecting realistic view of outcomes after tandem autologous or allogeneic transplantation.

Allogeneic HCT in MM has evolved over time. Myeloablative transplants have been replaced by RIC to reduce treatment related mortality while maintaining GVM effect. Immunomodulatory drugs such as lenalidomide can potentiate immunologic effects of allogeneic donor cells as seen by the high rate of development of GVHD in the HOVON 76 trial.[23] Lenalidomide was also used in the EBMT NMAM 2000 study for progressive disease after alloHCT wherein it was first noted that the post-relapse OS was superior in auto/RIC allo compared to auto/auto transplant group.[16] It is thus possible that an improved response to salvage therapy may occur in a donor-derived immunologic milieu that is potentiated by the immune effects of agents such as lenalidomide and pomalidomide. As noted by Wolschke et al,[24] post-alloHCT lenalidomide induces both NK and T cell mediated antimyeloma activity. Kneppers et al,[23] also showed that post-alloHCT lenalidomide increased the frequency of HLA-DR + T cells indicating T cell activation. In addition, substantial increase in NK cells displaying activated phenotype indicating postallograft immunemodulation is feasible. The role of DLI as a form of immune manipulation postallograft relapse and its efficacy in MM is well established[25] and Kroger, et al[26] have pioneered the use of donor lymphocytes and novel agents to potentiate the immune effect of allografts in order to augment myeloma responses.Our study indicated early relapses in immediate post allo HCT setting. One of the ongoing trials for high risk MM patients, BMT CTN 1302 (NCT02440464) includes Bortezomib to the conditioning regime and uses ixazomib vs. placebo as a maintenance after an allo HCT to evaluate whether such treatment can reduce relapse. With the availability of other agents that modulate immune mediated disease control such a daratumumab (reduction in T and B regulatory subsets)[27] and checkpoint inhibitors,[28] we hypothesize that post-alloHCT immune manipulation can further augment GVM immune effects and should be studied in clinical trials. Finally, the early relapse after allo HCT in our study also demonstrates that immunologic effect against MM may take time to occur and early immune manipulation after transplant may be a logical design in future clinical trials.

Acknowledgements

The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U10HL069294 from NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-13-1-0039 and N00014-14-1-0028 from the Office of Naval Research; and grants from *Actinium Pharmaceuticals; Allos Therapeutics, Inc.; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; *Blue Cross and Blue Shield Association; *Celgene Corporation; Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Fresenius-Biotech North America, Inc.; *Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.;*Gentium SpA; Genzyme Corporation; GlaxoSmithKline; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Jeff Gordon Children's Foundation; Kiadis Pharma; The Leukemia & Lymphoma Society; Medac GmbH; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; *Milliman USA, Inc.; *Miltenyi Biotec, Inc.; National Marrow Donor Program; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Perkin Elmer, Inc.; *Remedy Informatics; *Sanofi US; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; St. Baldrick's Foundation; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; *Tarix Pharmaceuticals; *TerumoBCT; *Teva Neuroscience, Inc.; *THERAKOS, Inc.; University of Minnesota; University of Utah; and *Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

Legend

Supplemental table 1 Selected publication review (auto/allo vs auto/auto)

Supplemental table 2 Selection criteria for study

Supplemental table 3 Univariate survival analysis of DLI vs. No DLI in post relapse AUTO/ALLO patients

Supplemental table 4 Treatment Related Mortality (TRM) of patients who had AUTO/ALLO & AUTO/AUTO transplants (time 0 at the 2nd TX)

Supplemental table 5 Adjusted post-relapse OS

Supplemental table 6 Novel agents used for induction chemo before 1st HCT

Supplemental table 7 Post transplant maintenance therapy

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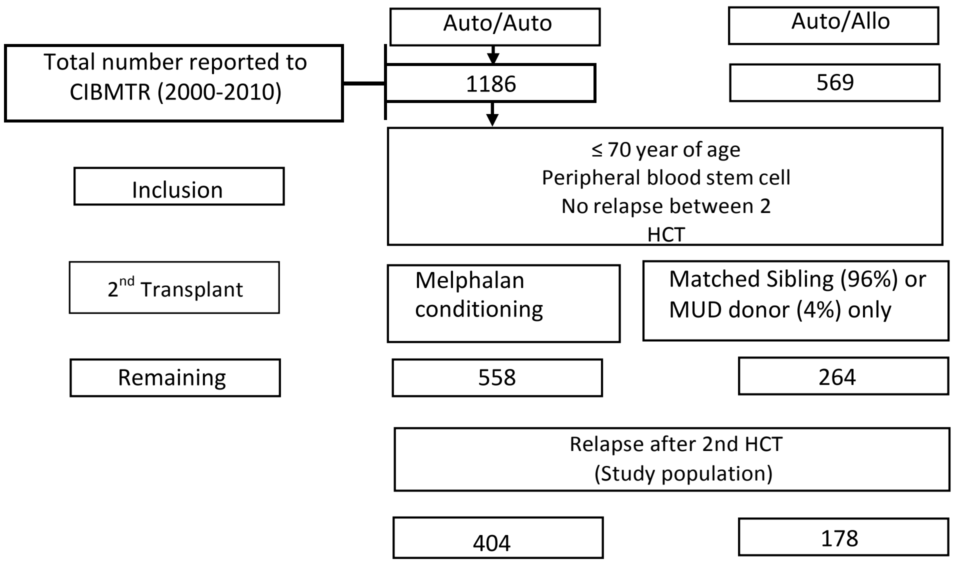
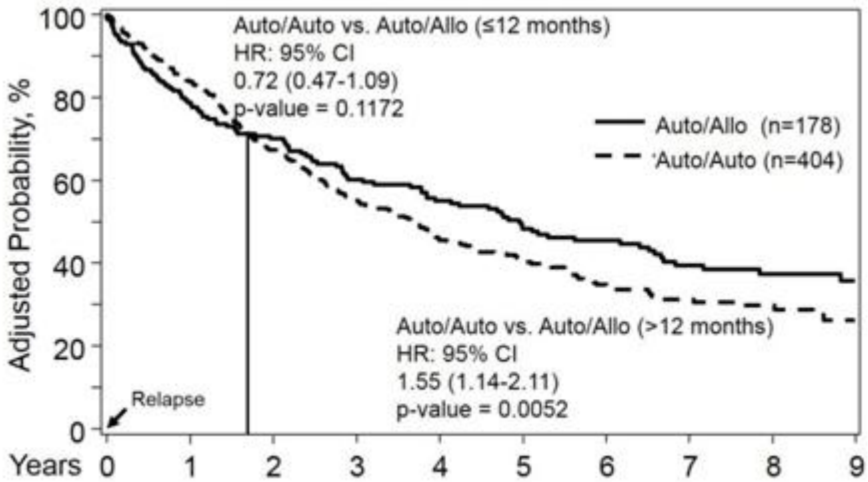
Figure 1. Overview of patient selection criteria



Auto, autologous; Allo, allogeneic; CIBMTR, Center for International Blood and Marrow Transplantation Research; HCT, hematopoietic stem cell transplantation; MUD, matched unrelated donor

Figure 2. Adjusted post-relapse overall survival



Number at risk

Auto/Allo	**178**	**137**	**118**	**97**	**85**	**71**	**61**	**56**	**43**	**33**
Auto/Auto	404	323	233	176	133	100	75	61	52	39

Table 1. Baseline characteristics of patients who relapsed after auto/allo or auto/auto HCT

Variable	Auto/allo	Auto/auto	P-value
Number of patients	178	404	
Number of centers	51	63	
Patient-related			
Age at 1st HCT, years			<0.001
Median (range)	51 (29-69)	56 (23-70)	
< 45	38 (21)	49 (12)	
45-60	119 (67)	248 (61)	
61-70	21 (12)	107 (26)	
Gender			0.66
Male	104 (58)	244 (60)	
Female	74 (42)	160 (40)	
Race			0.002
Caucasian	126 (71)	308 (76)	
Others	37 (21)	85 (21)	
Missing	15 (8)	11 (3)	
Karnofsky Score at 2nd HCT			0.05
>= 90%	126 (71)	244 (60)	
< 90%	37 (21)	111 (27)	
Missing	15 (8)	49 (12)	
Clinical trial enrollment			0.25
Yes	98 (55)	243 (60)	
No	80 (45)	161 (40)	
Disease-related			
Immunochemical subtype at diagnosis			0.14
IgG	116 (65)	226 (56)	
IgA	27 (15)	98 (24)	
Light chain	26 (15)	65 (16)	
Non-secretory	2 (1)	6 (1)	
Others	4 (2)	6 (1)	
Unknown type	3 (2)	3	
ISS/DS risk at diagnosis			0.18
Stage III	111 (62)	228 (56)	
Stage I-II	64 (36)	159 (39)	
Missing	3 (2)	17 (4)	
Cytogenetics risk*			0.07
High risk	9 (5)	21 (5)	
Standard risk	107 (60)	280 (69)	
Missing	62 (35)	103 (25)	
1st transplant-related			
Lines of chemotherapy prior to 1st HCT			<0.001
1	80 (45)	248 (61)	
2	49 (28)	116 (29)	
3+	19 (11)	35 (9)	
Missing	30 (17)	5 (1)	
Chemotherapy prior to 1st HCT#			<0.001
VTD/VRD/VCD	36 (20)	74 (18)	

Variable	Auto/allo	Auto/auto	P-value
TD,RD,VD	68 (38)	219 (54)	
VAD or others	33 (19)	106 (26)	
Missing	41 (23)	5 (1)	
Conditioning regimen for 1st HCT			<0.001
Melphalan	130 (73)	393 (97)	
Melphalan + Amifostine	3 (2)	3 (1)	
Melphalan + Topotican	1 (1)	0	
Missing	44 (24)	8 (2)	
Melphalan only	128 (72)	393 (97)	
Others	9 (4)	8 (2)	
Missing	41 (23)	3(1)	
Disease status prior 1st HCT			<0.001
CR	12 (7)	35 (9)	
PR	133 (75)	321 (79)	
SD/MR	18 (10)	44 (11)	
REL/PROG	2 (1)	4 (1)	
Missing	13 (7)	0	
Time from diagnosis to 1st HCT			0.09
Median (range)	8 (4-51)	7 (4-147)	
< 6 months	44 (25)	138 (34)	
6 - 12 months	111 (62)	213 (53)	
12 - 24 months	16 (9)	42 (10)	
Time from 1st Chemo to 1st HCT			0.09
Median (range)	7 (2-58)	6 (1-76)	
< 6 months	58 (32)	182 (45)	
6-12 months	99 (55)	194 (48)	
12-24 months	12 (7)	22 (5)	
> 24 months	6 (3)	6 (1)	
Missing	3 (2)	0	
Year of 1st HCT			<0.001
1999	1 (<1)	1 (<1)	
2000	5 (3)	8 (2)	
2001	11 (6)	2 (<1)	
2002	8 (4)	3 (<1)	
2003	9 (5)	6 (1)	
2004	44 (25)	81 (20)	
2005	31 (17)	134 (33)	
2006	42 (24)	92 (23)	
2007	18 (10)	35 (9)	
2008	4 (2)	24 (6)	
2009	5 (3)	11 (3)	
2010	0	7 (2)	
2nd transplant-related			
GVHD prophylaxis			
TAC + MMF +- other(s)	16 (9)		
TAC + MTX +- other(s)	18 (10)		
CSA + MMF +- other(s)	115 (65)		

Variable	Auto/allo	Auto/auto	P-value
CSA + MTX +- other(s)	9 (5)		
Others/Missing	20 (11)		
Donor type for ALLO			
HLA-matched related	170 (96)		
HLA-matched unrelated	8 (4)		
Melphalan dose for 2nd AUTO HCT(mg/m^2)			
Low dose-140		94 (23)	
High dose-200		296 (73)	
Unknown		14 (3)	
Disease status prior 2nd HCT			0.27
CR	33 (19)	56 (14)	
PR	125 (70)	308 (76)	
SD/MR	20 (11)	40 (10)	
Time from diagnosis to 2nd HCT months	10.8 (4.9-53.3)	10.9 (6.5-152.2)	
Time from 1st HCT to 2nd HCT			0.03
< 3 months	69 (39)	119 (29)	
3-6 months	109 (61)	285 (71)	
Conditioning for ALLO HCT			
Myeloablative	2 (1)		
Reduced Intensity	153 (86)		
Missing	23 (13)		
DLI post 2nd HCT (for ALLO)			
No	160 (90)		
Yes	18 (10)		
Post-transplant maintenance therapy†			<0.001
Novel agents	14 (7.8)	108 (26.8)	
Other agents (steroids, Cytoxan)	2 (1)	8 (1.9)	
None	107 (60)	154(38.1)	
Missing	55 (31)	134(33.1)	
aGVHD II-IV for ALLO relapse			<0.001
Yes	42 (24)		
No	134 (75)		
Missing	2 (1)		
aGVHD III-IV for ALLO relapse			<0.001
Yes	19 (11)		
No	156 (88)		
Missing	3 (2)		
cGVHD for Allo HCT relapse			0.04
Yes	103 (58)		
No	75 (42)		
Time from 2nd HCT to relapse, months			0.01
Median (range)	9 (0.10-98)	18 (0.13-112)	
< 6	81 (46)	105 (26)	
6-12	21 (12)	45 (11)	
12-24	33 (19)	96 (24)	

> 24	43 (24)	158 (39)
Median follow-up of survivors (range), months	102 (15-171)	99 (7-137)

AUTO, autologous; ALLO, allogeneic; HCT, hematopoietic stem cell transplantation; ISS, International Staging System; DS, Durie-Salmon; Novel agents include thalidomide, lenalidomide, bortezomib, pomalidomide and carfilzomib; V= Velcade (Bortezomib), T=Thalidomide, R= Revlimid (Lenalidomide), C= Cytoxan, D= Dexamethasone, VAD, vincristine, Adriamycin, and dexamethasone; CR, complete response; PR, partial response; SD, stable disease; MR, minor response; REL/PROG, relapse/progression; TAC, tacrolimus; MTX, methotrexate; MMF, mycophenolate mofetil; CSA, cyclosporine; HLA, human leukocyte antigen; DLI, donor lymphocyte infusion; aGVHD=acute graft vs. host disease, cGVHD=chronic graft vs. host disease

* High risk myeloma was defined as del17p, t(4;14), t(14;16), hypodiploidy (<45 chromosomes excluding -Y) or chromosome 1 p and 1q abnormalities.

Supplemental table 6: Novel agents used for induction chemo before 1st HCT

† **Supplemental table 7: Post transplant maintenance therapy**

Table 2. Post-Relapse survival of patients who relapsed post tandem transplant (Univariate Analysis)

	Auto/allo (N = 178)		Auto/auto (N = 404)		
Outcomes	**N Eval**	**Prob (95% CI)**	**N Eval**	**Prob (95% CI)**	**p-value†**
Overall survival post relapse	178		403		0.14‡
1-year		78 (72-84)%		84 (80-87)%	0.13
2-year		69 (62-76)%		67 (62-72)%	0.59
3-year		59 (52-67)%		55 (50-60)%	0.36
4-year		54 (46-62)%		46 (41-51)%	0.09
5-year		48 (40-56)%		41 (35-46)%	0.13
6- year		44 (37-52)%		35 (29-40)%	0.05

† Pairwise comparison p-value
‡ Log-rank test p-value
AUTO, autologous; ALLO, allogeneic; N, number, Prob, probability; CI, confidence interval

Table 3. Cause of death of patients who relapsed post tandem transplant

Cause of Death	Auto/allo (n=178)	Auto/auto (n=404)
Number of death	101	229
Primary disease	70 (69)	189 (83)
GVHD	4 (4)	0
Infection	16 (16)	8 (3)
Organ failure	4 (4)	9 (4)
Hemorrhage	0	2 (1)
Unknown	7 (7)	21 (9)

AUTO, autologous; ALLO, allogeneic; GVHD, graft-versus-host disease

Table 4. Multivariate analysis of OS from relapse in patients who relapsed post tandem transplant

Effect			Hazard Ratio	95% CI	Pairwise p-value	Overall p-value
Type of transplant	≤12 months after relapse	auto/allo	1			0.0040
		auto/auto	0.72	(0.47,1.087)	0.12	
	>12 months after relapse	auto/allo	1			
		auto/auto	1.55	(1.14,2.11)	0.0052	
Sex		Male	1			
		Female	1.27	(1.02,1.58)	0.030	
Clinical trial enrollment		Yes	1			
		No	1.39	(1.11,1.75)	0.0051	
Induction Chemotherapy		Novel Agent	1			0.017
		VAD/Others	1.43	(1.12,1.71)	0.0023	
		Missing	1.15	(0.73,1.79)	0.54	

CI, confidence interval; VAD, vincristine, Adriamycin and dexamethasone