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COMPARISON OF TWIN AND AUTOLOGOUS TRANSPLANTS FOR MULTIPLE MYELOMA

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Abstract

Relapse is the overwhelming cause of treatment-failure after autologous transplantation for multiple myeloma (MM). For patients with a syngeneic donor, twin transplants provide a healthy graft that is free of myeloma. The relative impact of the graft on post-transplant relapse can be estimated by comparing risk of relapse after hematopoietic cell transplantation from genetically-identical twins vs. autotransplants since confounding differences in minor or major histocompatibility antigens are absent in the syngeneic transplant setting. Outcomes of 43 subjects who received twin transplants for MM were compared to 170 matched autotransplant recipients reported to the CIBMTR. Multivariate analysis was performed by fitting a Cox model stratified on matched-pairs. The matched transplant patients studied were similar with respect to subject-, disease- and transplant-related characteristics. Cumulative incidence of relapse/progression was significantly lower and progression-free survival was significantly higher following twin transplants. In multivariate analysis, the probability of relapse/progression was lower in twins (relative risk, RR=0.49, 95% confidence interval (CI) 0.28 – 0.86, p=0.011). Twin transplants have a significantly lower relapse risk than autotransplants in multiple myeloma suggesting that graft composition may impact outcomes following high-dose chemotherapy.

Keywords

twin; autotransplant; multiple myeloma; graft-versus-myeloma

INTRODUCTION

Autologous hematopoietic cell transplants (HCT) are a common therapy with multiple myeloma (1,2). However, relapse/progression is common: actuarial post-transplant relapse/progression rates at 5 years exceed 90% in most series. Post-transplant relapse can occur because of persisting myeloma cells in the recipient, myeloma cells contaminating the autograft or both. Myeloma cells are commonly detected in autologous grafts (3–9); but the extent to which this contributes to post-transplant relapse is unclear. Studies correlating the degree of myeloma contamination of the autograft with outcome have produced contradictory conclusions (8,10). Attempts to reduce post-transplant relapse by decreasing myeloma cells in the graft have also been unsuccessful (11–13). Comparison of post-transplant relapse risk after syngeneic versus autlogous transplants (14,15) provide a basis for estimating the relative contribution of the graft on post-transplant relapse after autotransplants.

We analyzed outcomes of all evaluable recipients of genetically-identical twin transplants for multiple myeloma reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) between 1988 and 2003 and compared these to outcomes in a similar population receiving autologous HCT during the same period.

SUBJECTS AND METHODS

Data Sources

The CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR) and the National Marrow Donor Program (NMDP) that comprises a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplants to a Statistical Center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee or the NMDP Coordinating Center in Minneapolis.

Participating centers are required to report all consecutive transplants; compliance is monitored by on-site audits. Subjects are followed longitudinally, with yearly follow-up. Computerized checks for errors, physicians' review of submitted data and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are done with a waiver of informed consent and in compliance with HIPAA regulations as determined by the Institutional Review Board and the Privacy Officer of the Medical College of Wisconsin.

The CIBMTR collects data at two levels: registration and research. Registration data include disease type, age, sex, pretransplant disease stage and chemotherapy-responsiveness, date of diagnosis, graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, post-transplant disease progression and survival, development of a new malignancy and cause of death. Requests for data on progression or death for registered patients are at six-month intervals. All CIBMTR teams contribute Registration data. Research data are collected on a subset of registered patients selected using a weighted randomization scheme and include detailed disease, and pre- and post-transplant clinical information.

Subjects

Between 1988 and 2003, 80 recipients of genetically-identical twin transplants for MM were reported to the CIBMTR. Comprehensive subject-, disease-, and transplant-related characteristics were available for 47 patients. Characteristics and survival of twin transplant recipients with or without comprehensive data were similar (survival at 5 years, 58% (95% confidence interval [CI], 42–73%) vs. 67% (32–94%), pointwise p=0.64, log-rank p-value=0.15). Subjects receiving tandem transplants (defined as a planned 2nd transplant or a 2nd transplant within 6 months of the first without myeloma-relapse or -progression in between) were excluded from analysis as were grafts using CD34+ selection. The remaining 43 twin transplant recipients were matched to subjects receiving autologous transplants. There were 1801 recipients of autologous transplants for MM available for matching. To adjust for potential imbalance of risk factors between the cohorts, each twin transplant recipient was matched with up to four autologous transplant recipients as described below (Statistical Analysis section). The final study cohort consists of 43 twin transplant and 170 autologous transplant recipients. Eligible cases and controls came from 82 reporting centers from 20 countries. Median follow-up of survivors was 88 months for twins vs. 85 months for autotransplant recipients.

Endpoints

The primary endpoint was relapse/progression and secondary endpoints, treatment-related mortality (TRM), progression-free survival (PFS) and survival. Myeloma- relapse or -progression was defined as 25% increase either in measurable lesions, bone marrow plasmacytosis or M-protein level. TRM was defined as death from any cause within 28 days post-transplant or death of any cause thereafter without evidence of relapse or progression.

Treatment failure (inverse of PFS) was defined as the time from transplant to relapse or death from any cause. For analyses of survival, failure was death from any cause; survivors were censored at date of last contact.

Statistical Analyses

A propensity score indicating the predicted probability of receiving a specific treatment (twin vs. autologous transplant) was calculated conditional on the following key covariates using logistic regression modeling. The key risk factors used in fitting the logistic-regression model were age, Durie-Salmon stage at diagnosis, sensitivity to chemotherapy prior to transplant, time from diagnosis to transplant, and year of transplant. The numerical propensity scores for recipients of twin transplants ranged from 0.004 – 0.286. Twin recipients (cases) were then

matched in random order to autotransplant (control) recipients with similar propensity scores with the goal of obtaining up to 4 matched controls for each case. Matching involved the steps detailed below: (1) Twin transplant recipients were selected randomly. Any autotransplant recipient with a difference in propensity score less than ***0.07=(0.286−0.004)/4*** was considered a potential matched control; (2) The matched control with the smallest difference in propensity score among all potential matched controls was selected; (3) Step 1 was repeated among the remaining cases; (4) Steps 1–3 were repeated four times. The final matched cohorts included 43 twin transplant recipients and 170 autotransplant recipients (42 cases were found with 4 matches and 1 case with 2 matches). Baseline subject-, disease- and transplant-related variables for the twin and the matched autologous groups were compared using conditional logistic regression method to adjust the matching pairs.

Probabilities of PFS and survival were calculated using the Kaplan-Meier estimator; TRM and relapse/progression were calculated using cumulative incidence estimates. Estimates of standard error for the survival function were calculated by Greenwood formula and 95% CI, using log-transformed intervals. The log-rank test was used for univariate comparisons. Multivariate analysis was performed by fitting a Cox model stratified on matched-pairs. To further adjust for potential imbalance of risk factors between twin and auto transplant cohorts, a backward stepwise model building procedure was used to identify other risk factors associated with the outcome. The variables listed in Table 1 except those used in the modeling of the propensity score were used to build the final model. Any risk factors found to be significant were adjusted in the final Cox model stratified on matched pairs. All p-values are two-sided.

RESULTS

Subject Characteristics

Characteristics of subjects receiving twin transplant and controls receiving autotransplants are summarized in Table 1. The groups were well-matched with respect to subject-, disease and transplant-related characteristics. Twin transplant recipients were more likely to receive bone marrow grafts vs. peripheral blood cell grafts (44% vs. 8%; $p<0.001$). Graft type had no significant impact on any transplant outcome (data not shown). The difference in immunochemical subtype between the two groups was related to the larger number of patients in the twin group whose subtype was not specified and not due to differences in the frequency of any specified subtype. Sufficient data to determine International Staging System (ISS) stage at diagnosis was available for 19 twin and 89 autotransplant recipients; The ISS stage was not significantly different between twin transplant and autotransplant patients ($p=0.08$).

Furthermore, outcome parameters were not significantly different between subjects in whom ISS stage was or was not determined (data not shown). Cytogenetic data were not available for most subjects and was not considered in multivariate analyses. Two twin transplant recipients in our study were reported to have developed GVHD. One of them had limited skin involvement that resolved before day 100 and the other had liver function abnormalities that persisted beyond day 100 and then resolved.

Univariate Analysis

Cumulative incidence of relapse/progression was significantly lower in twin transplant recipients than autotransplant recipients at 1 year (10% (95% CI, 3–20%) vs. 26% (95% CI, 19–33%), $p=0.004$); 3 years (40% (95% CI, 25–55%) vs. 59% (95% CI, 51–66%), $p= 0.026$) and 5 years (43% (95% CI, 28–59%) vs. 71% (95% CI, 64–78%), $p=0.002$) (Figure 1). Cumulative probability of TRM at 1,3 and 5 years for twin transplant recipients was 14% (95% CI, 6–26%), 14% (95% CI, 6–26%) and 14% (95% CI, 6–26%) compared to 7% (95% CI, 4–

12%), 9% (95% CI, 5–13%) and 9% (95% CI, 5–13%)) for autotransplant recipients (p=NS for all time points). Long term PFS was better in twin recipients by log-rank comparison (p=0.023) and by point-wise comparison at 5 years (42% (95% CI, 27–58%) vs. 20% (95% CI, 14–27%), p=0.011) (Figure 2); there was no significant difference at 1 and at 3 years. Survival was also significantly better for twin vs. autotransplant recipients by point-wise comparison at 5 years (60% (95% CI, 44–75%) vs. 40% (32–48%), p=0.028) but not at 1 and 3 years (Figure 3).

Multivariate Analysis

Results of the multivariate analysis using Cox proportional hazards regression stratified on matched-pairs to analyze outcomes of interest are shown in Table 2. Twin recipients were significantly less likely to have relapse/progression (RR=0.49; 0.28–0.86; p=0.011). Risk of treatment-failure (RR=0.64; 0.401.05; p=0.08), TRM (RR=2.31; 0.82–6.51; p=0.10) and survival (RR=0.68; 0.40–1.16, p=0.10) were not significantly different.

Long-Term Survival

Five of 213 subjects were alive after 10 years (Table 3). One twin and one autotransplant recipient are relapse-free survivors at 10.7 and 12.6 years respectively. Another twin transplant recipient relapsed 2.9 years after the 1st transplant but is in remission at 10.6 years after a second transplant from the same donor. No twin transplant-recipient surviving > 10 years post transplant was reported to have developed graft versus host disease (GVHD).

DISCUSSION

Our study shows that twin transplant recipients have a significantly lower risk of myelomarelapse/progression than autotransplant recipients. A smaller report from the European Group for Blood and Marrow Transplantation (EBMT) (15) has also suggested that twin transplant recipients have a significantly lower risk of myeloma-relapse/progression compared to autotransplant recipients. Our study confirms that observation using a larger sample size of twin transplants (43 patients versus 25) longer follow-up (median follow-up 88 months vs. 29 months) and stringent matching based upon Propensity Score. Our results are also consistent with a similar study by the CIBMTR in persons with low-grade non-Hodgkin lymphoma (NHL) (16) showing significantly lower relapse risk in twin versus autotransplant recipients in that disease.

Several prior studies have suggested that allogeneic transplants are associated with a lower relapse risk than autotransplants in myeloma (15–18). Our data suggest that a myeloma free graft can significantly alter post-transplant relapse-risk even in the absence of disparity in histocompatibility genes seen with allogeneic transplants. There are, however, some cautions. For example, our analysis was retrospective and cytogenetic data were not available on all patients. Although an imbalance in cytogenetic risk groups may explain the difference we found, this is unlikely to given the comparability of the twin transplant and autotransplant groups with respect to other patient and disease related factors.

Several factors may explain the lower relapse risk seen in twin transplant recipients. In contrast to autotransplants, grafts from twins are free of contamination from myeloma cells. Contamination of autologous grafts with myeloma cells is common (3–6,8,9,12,17). Some data correlate extent of graft-contamination to the likelihood of relapse (8). Interpretations of these data are complex. One conclusion from these is that removing myeloma cells from the graft may decrease post-transplant relapse-risk. However, a recent gene-marking study failed to demonstrate evidence of relapse from marked cells within the autograft although the sample size was rather small (19). Furthermore, randomized (13), and non-randomized (10,12) studies

of attempted purging of myeloma from the graft show no clear benefit. Whether this represents insufficient purging or other factors that confound the effect of graft manipulation is unclear. For example purging of the graft may also eliminate some immune effector cells that inhibit relapse post-transplant. Also, immune cells in the normal twin graft are likely to be healthy and could have a stronger anti-myeloma effect than recipient immune cells (in an autograft) which may be exposed to prior therapy. However, there are few data suggesting an effective immune-mediated anti-myeloma effect except in the setting of HLA-disparity (which does not apply here). Also, although GVHD has been reported in twin transplant recipients (15,20) it is difficult or impossible to diagnose accurately, as is the case in our study. In allogeneic transplants, graft-versus-myeloma effects are strongly correlated with moderate to severe GVHD (21,22). Thus it is unlikely that the mild GVHD reported in only two twin transplant recipients in this study is the predominant explanation for the lower relapse-risk. Similarly, although the twin transplant patients were significantly more likely to receive bone marrow versus peripheral blood grafts, no significant effect of graft type (marrow versus peripheral blood) on outcome was detectable on multivariate analysis. Furthermore, there are no data within the literature to suggest that in multiple myeloma marrow grafts are superior to peripheral blood grafts. Our study confirms previous reports of long-term myeloma-free survival after high-dose therapy and twin transplants in some patients (14,15).

The observed long-term TRM rate was higher among the twin transplants than the autotransplants (14% versus 7%, RR 2.31). Although this difference was not statistically significant due to the sample size, it may been related to the higher frequency of marrow versus peripheral blood grafts in the twins and may have reduced the benefit of the reduced relapse rate seen in the twins upon PFS and OS.

In summary, this largest reported study of syngeneic transplantation in myeloma confirms that twin transplants have a lower relapse risk than comparable autotransplants. The results seen in the twins may be the best that could potentially be achieved following autografts if all contaminating myeloma cells could be removed from the graft Although the exact mechanism behind the advantage demonstrated for twin transplants cannot be defined, lack of graft contamination with myeloma, subclinical graft-versus tumor effects that are independent of HLA-disparity, and a graft unexposed to prior therapy may all have contributed. Attempts to improve the outcome of autologous transplants in myeloma may need to address these mechanisms. Furthermore, reduction in the myeloma burden in the graft may be of greater significance if the total body burden of myeloma is more substantially reduced pre-transplant, as it may now be achieved using novel induction therapies.

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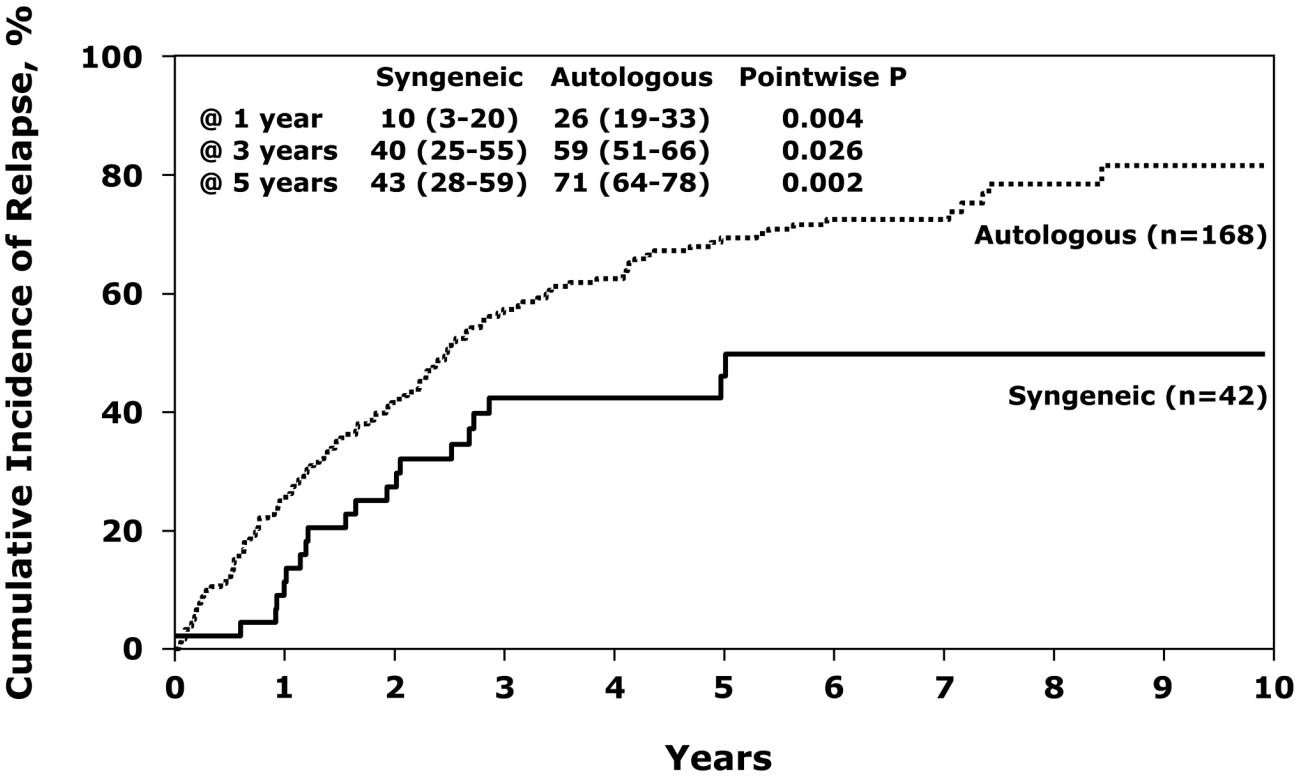

Figure 1.
Cumulative incidence of relapse after hematopoietic stem cell transplantation for multiple myeloma, by type of transplant.

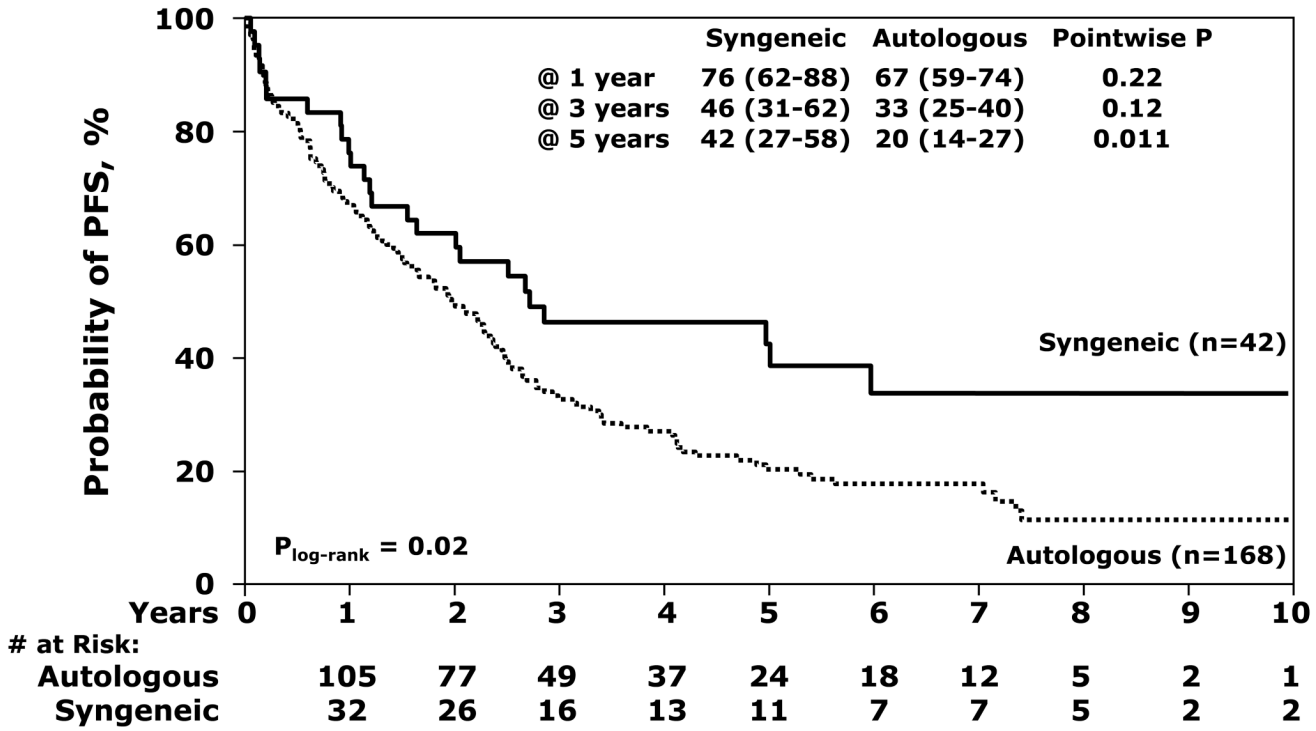

Figure 2.
Probability of progression-free survival after hematopoietic stem cell transplantation for multiple myeloma, by type of transplant.

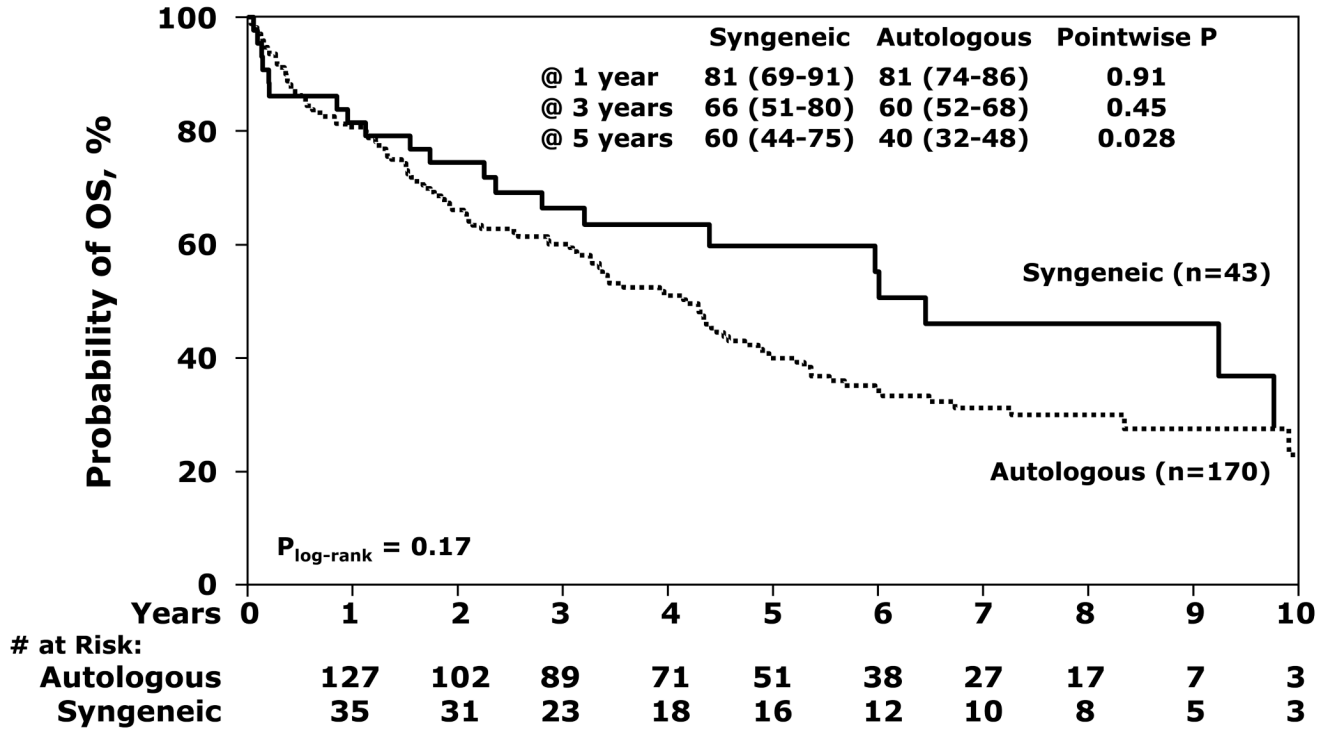

Figure 3.
Probability of overall survival after hematopoietic stem cell transplantation for multiple myeloma, by type of transplant.

Table 1

Characteristics of patients who underwent syngeneic or autologous first transplant for Multiple Myeloma.

Variable	Syngeneic N eval	Syngeneic N (%)	Autologous N eval	Autologous N (%)	P-value
Patient related					
Number of patients[a]		43		170	
Number of centers		36		54	
Age, median (range), years	43	53 (38 – 69)	170	52 (33 – 69)	0.57
Male sex	43	19 (44)	170	98 (58)	0.12
Karnofsky score pretransplant	43		159		0.59
<80		5 (12)		21 (13)	
80		8 (18)		34 (21)	
90–100		30 (70)		104 (66)	
Disease related					
Durie-Salmon stage at diagnosis	43		170		0.21
I		6 (14)		14 (8)	
II		15 (35)		65 (38)	
III		22 (51)		91 (54)	
ISS at diagnosis	19		89		0.08
I		3 (16)		31 (35)	
II		10 (53)		41 (46)	
III		6 (31)		17 (19)	
Immunochemical subtype of myeloma	43		170		0.004
IgG		17 (40)		96 (56)	
IgA		8 (19)		34 (20)	
Light chain		7 (16)		23 (14)	
Non-secretory		2 (4)		12 (7)	
Secretory – others /unknown		9 (21)		5 (3)	
Creatinine at diagnosis > 2 mg/dL	32	6 (19)	125	21 (17)	0.69
Radiation prior to transplant	43	9 (21)	170	56 (33)	0.13
Number of lines of chemotherapy prior to transplant	43		166		0.19
1		18 (42)		85 (51)	
2		13 (30)		54 (33)	
>2		12 (28)		27 (16)	
Disease status prior to transplant	42		156		0.31
Complete remission		7 (17)		25 (16)	
Partial remission		21 (50)		75 (48)	
Minimal response/Stable		13 (31)		45 (29)	
Relapse / Progression		1 (2)		11 (7)	
Sensitivity to chemotherapy prior to transplant	43		170		0.81
Sensitive		26 (60)		105 (62)	
Resistant		17 (40)		65 (38)	
Creatinine prior to transplant > 2 mg/dL	43	4 (9)	162	10 (6)	0.42
Transplant related					
Time from diagnosis to transplant	43		170		0.20
<12 months		26 (60)		112 (66)	
≥12 months		17 (40)		58 (34)	
Conditioning regimen	43		170		0.57
Melphalan based – No TBI		17 (40)		84 (49)	
Melphalan+TBI±others		9 (20)		44 (26)	
No TBI / No Melphalan (Bu+Cy & others)[b]		17 (40)		42 (25)	
Graft type	43		170		<0.001
BM		19 (44)		14 (8)	
PBSC±BM		24 (56)		156 (92)	
Year of transplant	43		170		0.51
1988–1992		7 (16)		25 (15)	

Variable	Syngeneic N eval	Syngeneic N (%)	Autologous N eval	Autologous N (%)	P-value
1993–1997		17 (40)		74 (43)	
1998–2003		19 (44)		71 (42)	
Planned therapy post transplant[c]	43	15 (35)	170	78 (46)	0.22
Median follow-up of survivors, median (range)		88		85	

Abbreviations: ISS = International Staging System; BU = busulfan; CY = cyclophosphamide; TBI = total body irradiation; LPAM = melphalan; BM = bone marrow; PBSC = peripheral blood stem cells; EVAL = evaluable.

[a] Three years of complete follow-up [syngeneic (88%); autologous (92%)]
Four years of complete follow-up [syngeneic (84%); autologous (91%)]

[b] The other conditioning regimens for the autologous group were: busulfan+cyclophosphamide (n=34); other TBI containing regimen (n=5); Cy+etoposide+BCNU (n=1); Cy+etoposide (n=1) and Cy +etoposide+BCNU+DTIC (n=1). The other conditioning regimens for the syngeneic group were: busulfan+cyclophosphamide (n=10); other TBI containing regimen (not LPAM) (n=7).

[c] The type of planned post transplant therapy for the syngeneic group were: interferon±others (n=9); thalidomide±others (n=1); biphosphonates±others (n=1) and others, not specified (n=4). The types of planned post transplant therapy for the autologous group were: interferon±others (n=43); IL2/Immunotherapy±others (n=3); thalidomide±others (n=2); biphosphonates±others (n=14); radiation±others (n=1) and others, not specified (n=15).

Table 2

Relative risks of relapse, treatment-related mortality, treatment failure and mortality with autologous vs. syngeneic transplants in multivariate analysis.*

Outcome event	Relative Risk (95% CI)	P-value[b]
Treatment Related Mortality		
Autologous	1.00[a]	
Syngeneic	2.31 (0.82 – 6.51)	0.10
Relapse/progression		
Autologous	1.00[a]	
Syngeneic	0.49 (0.28 – 0.86)	0.011
Treatment failure		
Autologous	1.00[a]	
Syngeneic	0.64 (0.40 – 1.05)	0.08
Mortality		
Autologous	1.00[a]	
Syngeneic	0.68 (0.40 – 1.16)	0.15

[a] Reference group

[b] Score test

* Multivariate results are based on fitting a Cox model stratified on matched pairs.

Table 3

Long term survivors following syngeneic or autologous transplantation

Transplant	Time to relapse, years	Status at last contact date	Time from tx to last contact date, years
Autologous	no	CR	12.6
Autologous	7.4	PR	12.1
Autologous	5.3	NR/SD	10.14
Syngeneic	2.9	CR	13.45
Syngeneic	no	CR	10.7

Abbreviations: TX = transplant