Title: Costs of second allogeneic hematopoietic cell transplantation

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Abstract

Graft failure, disease recurrence and secondary malignancy are the main indications for a second allogeneic transplant following a prior allogeneic (allo-allo) or autologous (auto-allo) hematopoietic cell transplantation (HCT). Reported outcomes are generally poor, especially for the allo-allo group. The role of planned tandem auto-allo transplants for myeloma and lymphoma is continuing to evolve. Our objective was to describe the cost profile of second HCT and evaluate the relationship between total costs, baseline patient characteristics and post-transplant complications. Clinical information and medical costs of 245 patients (allo-allo: 55, auto-allo: 190) who underwent a second HCT at Fred Hutchinson Cancer Research Center between 2004 and 2010 were collected. Linear regression was used to evaluate the associations between baseline patient characteristics, clinical events and costs for the first 100 days after transplantation. Median costs of the second allogeneic HCT were $151,000 (range $62,000-405,000) for the allo-allo group and $109,000 (range $26,000-490,000) for the auto-allo; there was no difference between the costs in the auto-allo group whether done as a planned tandem or as salvage for relapse. Median length of hospital stay was 23 days (range 0 - 76) for the allo-allo group and 9 days (range 0-96) for the auto-allo group. While HCT for graft failure in the allo-allo group and the use of myeloablative conditioning and unrelated or mismatched donors emerged as a significant predictor of costs in the auto-allo group when only pre-transplantation variables were considered, the year of transplant and post-transplant complications were significantly associated with costs in both groups when the post-transplant events were added to the model. Our results suggest that second allogeneic HCT is costly, particularly if it follows a prior allogeneic transplant, and is driven by the costs of complications.

Introduction

In the past, allogeneic transplants subsequent to a previous allogeneic (allo-allo) or autologous (auto-allo) transplant were used exclusively as a therapeutic treatment for graft failure, relapse of disease or occasionally the development of a different malignancy after the initial hematopoietic cell transplantation (HCT).(1) The last decade has also seen a substantial increase in the number of planned tandem auto-allo transplants for the treatment of myeloma and lymphoma, even though the efficacy of this strategy is still a matter of great controversy, especially in myeloma.(2) According to government statistics, HCT generated the greatest percentage increase in total hospital costs from 2004 to 2007, due primarily to an increase in the cumulative number of hospital stays.(3) The increase in number of hospital stays is likely because the procedure is more widely available due to reduced intensity conditioning regimens and better supportive care. This has led to inclusion of older and sicker individuals and the ability to perform multiple transplants in patients. The implementation of the Affordable Care Act may further accelerate the trend since it prohibits the health plans from setting lifetime dollar limits on the benefits, which may have previously limited second transplants. Approximately 15,000 allo-allo and 8300 auto-allo transplants were reported to the Center for International Blood and Marrow Transplant Registry between 2000 to 2010 (Tanya Pedersen, personal communication).

Multiple studies examining patient outcomes after a second allogeneic transplant reported an overall survival in the range of 20 to 40% at 3 years.(4-14) An exception has been planned tandem auto-allo transplants which have shown more favorable complete response rates and survival, though a recent phase III trial in myeloma showed an efficacy comparable to tandem autologous HCT.(15-18)

The decision to pursue a second allogeneic transplant has financial implications as well as clinical outcomes. Messori et al have looked at the cost effectiveness of

second allogeneic bone marrow transplantation in patients with relapsed acute leukemia based on published data from January 1985 to June 1998.(19) They showed that second HCT prolonged survival and was cost effective as compared to chemotherapy for relapse after an initial HCT. However the authors did not report a detailed analysis of costs in their report. Our study aimed to evaluate the clinical and economic outcomes of a second allogeneic HCT following a prior autologous or allogeneic transplant. We specifically sought to identify the main factors that are associated with costs in a modern cohort of patients.

Patients and Methods

Patients

This retrospective study included 245 patients who underwent an allogeneic transplant following a prior autologous or allogeneic HCT between 2004 and 2010 at a single large center. Patients gave consent allowing the use of medical records for research, and the Institutional Review Board at the Fred Hutchinson Cancer Research Center (FHCRC) approved the study.

Eighty four patients received their first transplant at another center, so the details and costs of the prior procedure were not available. In the allo-allo group, the second HCT was performed for recurrence of the original disease in 65% of patients and for graft failure in 25%. Fifty four percent of patients in the auto-allo group received the second HCT for relapsed disease, and 42% were planned tandem auto-allo transplants. For the remaining patients in both groups, the second HCT was done for a different indication than the original diagnosis (e.g., aplastic anemia after initial transplant for acute myeloid leukemia, treatment related myelodysplastic syndrome/ acute myeloid leukemia following an autologous HCT). The median time between the first and second

transplantations was 12.8 months (range, 1.5-186.2) in the allo-allo group and 9.6 months (range, 1.3-167.8 months) in the auto-allo group.

Conditioning, GVHD prophylaxis and supportive care for the second HCT

Myeloablative conditioning was used more frequently for the second HCT in the allo-allo group as compared to the auto-allo group (40% vs. 27%) Patients with aplastic anemia (AA) received cyclophosphamide and antithymocyte globulin. GVHD prophylaxis was per protocol and antimicrobial prophylaxis, blood product and nutritional support were provided per institutional guidelines.

Most non-myeloablative/ reduced intensity transplants were performed as outpatients with hospital admission only for cell infusion (if mandated by insurance or for stem cell products arriving when the outpatient clinic was closed). Patient were admitted to the hospital primarily for management of complications such as febrile neutropenia, severe GVHD requiring parenteral nutrition and iv medications, severe pain requiring intravenous narcotics, inability to maintain oral intake etc.

Patients receiving myeloablative regimens were admitted prior to the cell infusion or during the conditioning depending on the regimen, and discharge criteria were based on neutrophil engraftment, adequate oral intake, and medical stability.

Cost data

All charges (inpatient and outpatient) and total hospital days for the second HCT from D -7 of transplant to D+100 were retrieved from the administrative database. This information was also retrieved for the first HCT for patients who had received their first HCT at our institution. For the first autologous HCT, D -7 to D+30 was used as the time horizon for costs. If the interval between the two transplants was shorter, the upper limit for the first HCT costs was considered d -8 of the second HCT. Charges were converted

to costs using departmental ratios of charges to costs and adjusted to the year 2010 using the medical care component of the consumer price index.(20) Costs of donor identification and graft procurement were excluded. Professional charges, patient time and productivity costs, and direct non-medical costs (e.g. transportation, lodging) were not captured. Thus, this cost analysis reflects the perspective of the health care system.

Statistical Analysis

Cumulative incidence estimates were calculated for relapse, acute GVHD, and non-hematological toxicity, treating death as a competing risk. Cumulative incidence estimates of non-relapse mortality treated relapse as a competing risk. Overall survival was estimated using the Kaplan-Meier method. A descriptive analysis of the inpatient and outpatient costs for the first 100 days was done using numeric summaries (mean, variance, median, range). Pre-transplant and post-transplant predictors of costs were identified using multiple linear regression with year of transplant, patient (e.g. demographics, disease variables, CMV status) and transplant characteristics (e.g. stem cell source, HLA matching, donor type, conditioning regimen) entered first, and post-transplant complications (severe infections, VOD, pulmonary or renal complications) added second. Separate models were created for the allo-allo and the auto-allo groups.

Since distribution of costs is typically right skewed, the logarithm of costs was used for the multivariate analysis. Results are presented as 'cost multipliers' which are the ratios of costs of patients with specific baseline characteristics or experiencing the specific complication compared with those who do not. For example, a cost multiplier of 1.17 for relapse corresponds to a 17% increase in costs of patients who relapsed as compared to those who did not. All reported p-values are two-sided and p-values less than 0.05 were considered significant.

Results

Clinical characteristics of the study cohort

Table 1 summarizes the demographic, disease and transplant-related characteristics of the 245 patients. Median age at second HCT was 50 years (range, 21-68 years) in the allo-allo group and 51 years (range 18-72 years) in the auto-allo group. Three fifths of the study population was male in both groups. A higher proportion of patients received non-myeloablative/ reduced intensity conditioning in the auto-allo group as compared to in the allo-allo group (73% vs. 60%,). Median follow-up period from HCT was 19.8 months (range, 0.5-61.2 months).

Clinical Events and Outcomes

Engraftment occurred in 230 out of 245 patients and the median time to an absolute neutrophil count of ≥500/μl was 15 days (range, 6-49 days). The other clinical outcomes of GVHD, organ toxicity, relapse and causes of death for the first 100 days are shown in table 2. One year transplant-related mortality in this cohort was 15% and the relapse rate was 36%. Median follow-up time for the surviving patients was 19.8 months (range, 0.5-61.2 months). Figure 1 show the overall survival curves for the auto-allo and allo-allo groups according to the reason for second transplant.

Costs and predictors of costs

Table 3 shows the median costs for the first 100 days (30 days for the autologous HCT) after the first and second HCT. In the subset of the allo-allo group for which we had data for both transplants, the second allogeneic HCT was more expensive than the first (median 151,000 vs., 132,000; p=0.0004). Various categories of the costs are illustrated in figure 2.

In the multivariate analyses for the allo-allo group, there was no association of costs with age, disease, disease status, or conditioning regimen though graft failure as a reason for HCT was associated with higher costs when only pre-transplantation variables were considered. Use of myeloablative conditioning and unrelated or mismatched donors was a significant cost driver in the auto-allo group, but not in allo-allo group, in the model using only pre-transplant variables. Only mismatched donors remained significant when both pre and post-transplantation variables were considered. Among the post-transplant complications, acute GVHD, pulmonary complications and infection were associated with significantly increased costs in both groups while renal complications were significant only for the allo-allo group. Interestingly, while the year of transplant was associated with a 14% *decrease* in costs per year in the allo-allo group, a 4% *increase* per year was seen in the auto-allo group. (Tables 4 and 5)

Discussion

Second allogeneic HCT has been a therapeutic strategy to address relapse, graft failure or second malignancy after a prior HCT, or to try to achieve better disease control as part of planned tandem transplant after a prior autologous procedure. Our study evaluated two distinct cohorts of second allogeneic HCT (allo-allo and auto-allo) for costs of second HCT and described their association with pre-transplant characteristics and post-transplant complications. Similar to what has been shown for first HCT; we found that baseline patient characteristics do not help predict the costs except for mismatched donor transplants which were associated with higher costs in the auto-allo group. Additionally, post-transplant complications are significant cost drivers for second HCT in both the groups.(21) The outcomes of a second allogeneic HCT after a prior allogeneic HCT have generally been quite disappointing.(4) High transplant related mortality (TRM), ranging from 30 to 60%, is reportedly due to post-transplant infections

and regimen related toxicity.(7, 8, 11, 12) Our study shows that these complications also increase the cost of the procedure significantly. This may be the reason that even though the overall costs for the second HCT are in the range of reported costs in prior studies, the second allogeneic transplant was more expensive than the first allogeneic procedure in the allo-allo group,.(22)

Our study also described the outcomes and costs of allogeneic HCT following an autologous HCT. Similar to the allo-allo group, the overall costs for the autologous and allogeneic HCT are in the range of what has been described in the literature.(22) Interestingly, while there was a difference in costs between second HCT when done as a planned tandem auto-allo or for relapse of disease after a prior autologous HCT in univariate analysis (data not shown), this distinction lost its significance in the multivariate analysis, likely due to adjustment for patient and disease related characteristics.

A cost-effectiveness analysis using the upper range of published cost data from 1992 to 1996 for HCT showed an acceptable cost profile for second HCT done for relapse of leukemia as compared to chemotherapy.(19) The sensitivity analysis in this study explored the consequences of varying HCT costs and found that the cost per life year gained remained close to the acceptable threshold of $50,000 per quality adjusted life year gained if the transplant costs were ≤ $150,000 ($184,688 in 2010 dollars). A more recent descriptive cost study by Svahn et al showed that re-transplantation is associated with higher mean costs of the first HCT itself (relative hazard 1.21, p=0.001) , though the costs for second transplant were not separated from the first transplant.(23) This is similar to the solid organ literature where re-transplantation has also been shown to be associated with greater costs and worse survival, raising important ethical questions due to depletion of already limited supply of organs.(24) While the ethical dilemma is not quite as poignant in the field of blood and marrow transplantation since

the graft is usually not a limited resource, the question about high costs, optimum use of societal resources and ethics of second HCT has been raised by investigators.(6, 25)

In this era of increasing health care costs, consideration of second HCT especially for relapse should be made based on clinical effectiveness and economic impact of the projected outcome to optimize the utility of our scarce resources. This is especially relevant if non-transplant options may be available with no convincing evidence for one approach being better than others. Similarly, for the tandem auto-allo transplants, doing them outside a clinical study may result in widespread use before evidence of their effectiveness is available. This risks a similar experience as with the use of high dose therapy and autologous transplants for breast cancer, where public opinion, political influence and the threat of litigation resulted in coverage of this procedure by insurance companies even though eventually definitive clinical trial data showed no overall benefit and greater toxicity.(26)

Our study does have some limitations. The sample size was limited in the allo-allo group and may have prevented our ability to detect any associations between costs and clinical characteristics. We were missing some details that would have been helpful, such as information about co-morbidities and uniform follow-up cost data beyond day 100, since most patients return to the care of their local physician beyond 100 days. It is unknown if the rate of complications beyond 100 days is higher for second HCT since that would imply higher downstream costs also. Because this was a retrospective study, we did not have any information about how the second HCT adds on to the financial burden for patients and their families. Finally, the cost estimates reflect resource utilizations at our center and may not be representative because of differences in practice patterns, patient mix and accounting methodologies at different centers.

Despite the above limitations, our study provides valuable information that can be used to design economic analyses comparing prevention or treatment of relapse, graft

failure or second malignancy vs. second HCT. This study is one of the first to provide economic data on the tandem auto-allo transplants to build a framework for the economic assessment of this strategy. It provides estimates of direct medical costs to help design a cost-effectiveness analysis comparing the planned approach to salvage HCT for relapse. Finally, it characterizes the factors that are associated with higher costs of second HCT to help design interventions that would help improve clinical outcomes while helping to contain the costs. Efforts to improve the clinical outcomes further by decreasing the regimen related toxicity and recurrence rates of second transplant can not only help lower costs, but also improve the cost-effectiveness of the procedure further.

Our results suggest that the short-term costs of second transplants appear higher than those of first transplants especially for allo-allo transplants and the clinical outcomes have much room for improvement. Additional work is needed with larger numbers of patients to confirm the characteristics that would predict the group with the best clinical and economic outcomes. A careful assessment of both benefits and costs of expensive medical interventions such as second HCT is paramount for providing high-value and high-quality care while controlling the soaring healthcare costs.

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Table 1: Baseline clinical characteristics

Characteristic	Allo-Allo (n=55)	Auto-Allo (n=190)
Age (years)		
Median (range)	50 (21-68)	51 (18-72)
Males	34 (62)	114 (60)
Diagnosis		
AML/MDS/MPD	38 (69)	21 (11)
ALL	7 (13)	2 (1)
NHL/HD/CLL	6 (11)	108 (57)
Multiple Myeloma	0	59 (31)
Other	4 (7)	0
Reason for second transplant		
Tandem	0	80 (42)
Relapse	36 (65)	102 (54)
Graft failure	14 (25)	0
Other reasons including second malignancy	5 (9)	8 (4)
Disease status (3 missing)		
Relapse	22 (40)	134 (71)
Remission	33 (60)	56 (29)
Donor		
Matched related	10 (18)	72 (38)
Matched unrelated	31 (56)	63 (33)
Mismatched	14 (25)	55 (29)
Conditioning		
High intensity	22 (40)	52 (27)
Reduced intensity/ Non-myeloablative	33 (60)	138 (73)
Stem cell source		
PBSC	44 (80)	160 (84)
BM	5 (9)	28 (15)
Cord	6 (11)	2 (1)
CMV serostatus (7 missing)		
D+/R-	5 (10)	22 (12)
D+/R+	16 (32)	50 (27)
D-/R-	13 (26)	57 (30)
D-/R+	16 (32)	58 (31)
Months between transplants		
Median (range)	12.8 (1.5-186.2)	9.6 (1.3-167.8)

Abbreviations: HCT, Hematopoietic cell transplantation; Allo-allo, 2 allogeneic transplants; Auto-allo, autologous transplant followed by allogeneic transplant; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease; ALL, acute lymphoid leukemia; NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease; CLL, chronic lymphocytic leukemia; D, donor; R, recipient

Table 2: Clinical outcomes in first 100 days after second HCT

Variable N (%)	Allo-allo (n=55)	Auto-allo (n=190)
Cumulative incidence of relapse	14 (25)	40 (21)
Cumulative incidence of grades II-IV acute GVHD	34 (62)	128 (67)
Organ toxicity Pulmonary Veno-occlusive disease/sinusoidal obstructive syndrome Infections Renal/bladder	 10 (18) 8 (15) 29 (53) 9 (16)	 29 (15) 10 (5) 117 (62) 79 (42)
Number of deaths	13 (24)	24 (13)
Cause of death* Relapse Graft-vs.-Host disease Infection Other	 3 (23) 1 (7) 5 (38) 5 (38)	 3 (33) 5 (20) 6 (25) 9 (38)

*Sum of percentages >100% since multiple causes of death were listed for some patients

Abbreviations: HCT, Hematopoietic cell transplantation; Allo-allo, 2 allogeneic transplants; Auto-allo, autologous transplant followed by allogeneic transplant

Table 3: Costs and length of stay for the first 100 days after the first and second HCT*

	Allo-allo		Auto- allo	
	1st Allo (n=42)	2nd Allo (n=55)	Auto (n=119)	Allo (n=190)
Median total costs, $1000's (range)	132 (25-279)	151 (62-405)	72 (28-167)	109 (26-490)
Median Inpatient costs, $1000's (range)	76 (0-278)	92 (0-371)	43 (0-128)	22 (0-433)
Median Outpatient costs, $1000's (range)	60 (1-155)	68 (0-194)	29 (3-88)	72 (1-199)
Median hospital stay, days (range)	25 (0-47)	23 (0-76)	15 (0-34)	9 (0-96)

*For first 30 days after the autologous HCT

Abbreviations: Allo-allo, 2 allogeneic transplants; Auto-allo, autologous transplant followed by allogeneic transplant

Table 4: Linear regression for costs of second allogeneic HCT following a prior allogeneic transplant

Variable	Baseline model			Full model		
	Cost multiplier	95% CI	P value	Cost multiplier	95% CI	P value
Pre-transplant factors						
Age						
<50	1.0			1.0		
≥50	1.01	0.77-1.32	0.96	1.03	0.80-1.33	0.81
Disease						
Acute leukemia/MDS	1.0			1.0		
Lymphoma	1.07	0.68-1.68	0.77	0.89	0.59-1.34	0.57
Other	0.61	0.33-1.11	0.11	0.67	0.39-1.15	0.15
Disease status						
Remission	1.0			1.0		
Relapse	0.89	0.64-1.25	0.51	0.84	0.61-1.15	0.29
Graft source						
PBSC	1.0			1.0		
BM/Cord	1.27	0.83-1.94	0.28	1.36	0.92-1.99	0.13
Conditioning						
NMA	1.0			1.0		
MA	1.39	0.96-2.03	0.09	1.23	0.88-1.72	0.24

Reason for transplant						
Relapse	1.0			1.0		
Rejection/failure	**1.41**	**1.01-1.97**	**0.05**	1.25	0.93-1.69	0.14
Other	1.00	0.57-1.76	0.99	0.96	0.54-1.72	0.90
Year of transplant						
Per year	0.96	0.86-1.07	0.45	**0.86**	**0.78-0.95**	**0.005**
Donor type						
Matched related	1.0			1.0		
Matched unrelated	0.97	0.68-1.37	0.86	0.91	0.67-1.22	0.52
Mismatched	1.00	0.63-1.59	0.99	0.77	0.51-1.18	0.24
CMV serostatus						
Negative	1.0			1.0		
Positive	1.01	0.76-1.35	0.94	0.87	0.67-1.13	0.30
Post-transplant complications						
Death				0.70	0.46-1.06	0.10
Relapse				1.20	0.90-1.60	0.23
GVHD (II-IV)				**1.42**	**1.09-1.84**	**0.01**
SOS				0.92	0.63-1.33	0.66
Pulmonary				**1.55**	**1.12-2.16**	**0.01**
Renal				**1.90**	**1.16-3.10**	**0.02**
Infection				**1.42**	**1.10-1.85**	**0.01**

Abbreviations: MDS, myelodysplastic syndrome; PBSC, peripheral blood stem cells; BM, bone marrow; NMA, non-myeloablative; MA, myeloablative; CMV, cytomegalovirus; GVHD, graft vs. host disease; SOS, sinusoidal obstruction syndrome

Table 5: Linear regression for costs of second allogeneic HCT following a prior autologous transplant

Variable	Baseline model			Full model		
	Cost multiplier	95% CI	P value	Cost multiplier	95% CI	P value
Pre-transplant factors						
Age						
<50	1.0			1.0		
≥50	1.04	0.91-1.18	0.58	1.02	0.91-1.15	0.68
Disease						
Lymphoma	1.0			1.0		
Acute leukemia/MDS	1.05	0.81-1.35	0.71	1.09	0.87-1.36	0.47
Myeloma	0.87	0.74-1.02	0.09	0.94	0.82-1.09	0.44
Disease status						
Remission	1.0			1.0		
Relapse	1.07	0.91-1.25	0.40	1.03	0.90-1.19	0.66
Graft source						
PBSC	1.0			1.0		
BM/Cord	0.97	0.73-1.28	0.81	0.92	0.72-1.18	0.52

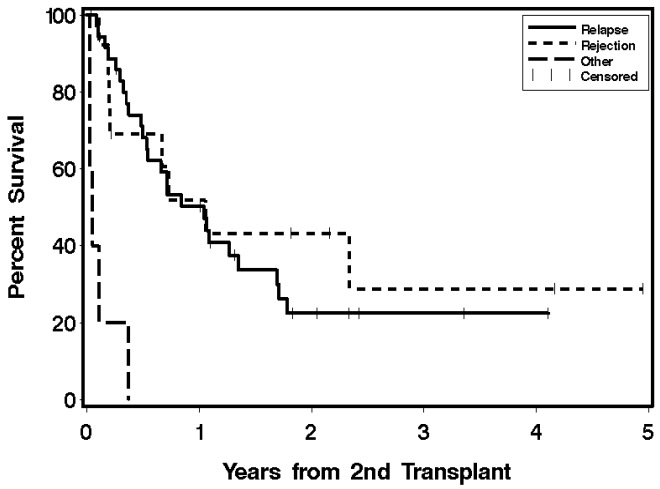
Conditioning						
NMA	1.0			1.0		
MA	**1.23**	**1.00-1.51**	**0.05**	1.13	0.94-1.35	0.21
Reason for transplant						
Relapse	1.0			1.0		
Tandem auto-allo	0.93	0.80-1.09	0.37	0.93	0.81-1.06	0.26
Secondary malignancy	0.78	0.53-1.14	0.20	0.82	0.59-1.15	0.25
Year of transplant						
Per year	**1.05**	**1.01-1.10**	**0.02**	**1.04**	**1.01-1.08**	**0.03**
Donor type						
Matched related	1.0			1.0		
Matched unrelated	**1.23**	**1.05-1.45**	**0.01**	1.12	0.97-1.29	0.12
Mismatched	**1.34**	**1.10-1.62**	**0.004**	**1.19**	**1.00-1.42**	**0.05**
CMV serostatus						
Negative	1.0			1.0		
Positive	1.10	0.96-1.25	0.17	1.01	0.89-1.13	0.91
Post-transplant complications						
Death				1.06	0.87-1.29	0.55
Relapse				1.02	0.89-1.18	0.73
GVHD (II-IV)				**1.15**	**1.02-1.30**	**0.03**

SOS				0.93	0.71-1.22	0.61
Pulmonary				**1.42**	**1.19-1.71**	**0.0002**
Renal				1.01	0.90-1.14	0.82
Infection				**1.38**	**1.21-1.57**	**<0.0001**

Abbreviations: MDS, myelodysplastic syndrome; PBSC, peripheral blood stem cells; BM, bone marrow; NMA, non-myeloablative; MA, myeloablative; auto-allo, autologous transplant followed by allogeneic transplant; CMV, cytomegalovirus; GVHD, graft vs. host disease; SOS, sinusoidal obstruction syndrome

Figure 1: Overall survival according to the indication for second hematopoietic cell transplant

A) Second allo HCT following a prior allogeneic transplant



B) Second allogeneic HCT following a prior autologous transplant

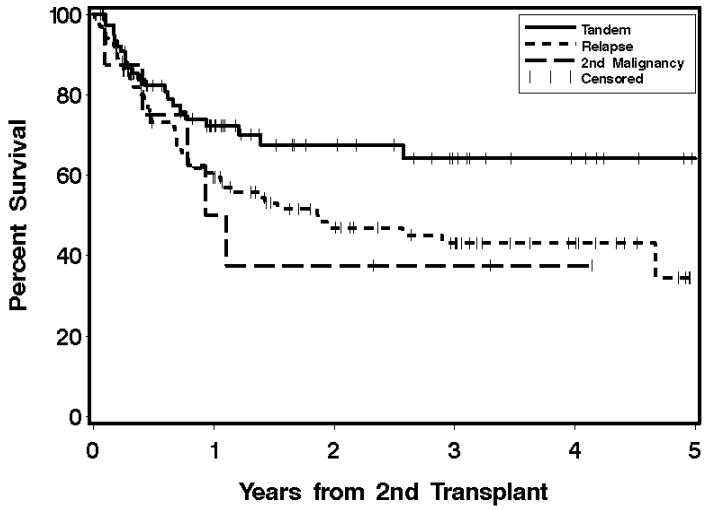
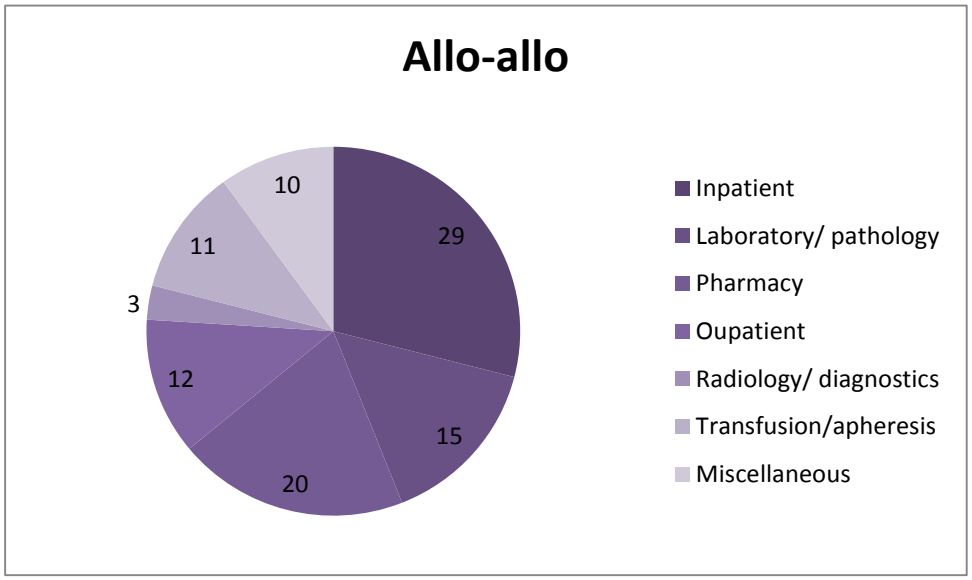


Figure 2: Categories of costs in the two groups

A) Allogeneic HCT following prior allogeneic transplant



B) Allogeneic HCT following prior autologous transplant